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NOTICE TO CONTRIBUTORS

The ACTA RHEUMATOLOGICA SCANDINAVICA
publishes papers on rheumatology

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Rosenthal L et al Acta Rheum Scand 17 3—14 1971

From the Dept of Rheumatology (Head B Olhagen)
and
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Karolinska Sjukhuset, Stockholm Sweden

A CLINICAL AND ROENTGENOLOGICAL FOLLOW UP STUDY OF PATIENTS WITH URO ARTHRITIS OR PELVOSPONDYLITIS

By

L ROSENTHAL C LAGERGREN and B OLHAGEN

Summary A clinical and radiological follow up investigation of 124 patients with uro arthritis or pelvospondylitis who had been under careful urological supervision and long term treatment with sulphonamides and/or antibiotics, showed good prognosis The part played by the treatment is discussed

It has long been known that there exists a relationship between urogenital infection and some rheumatic diseases This holds true not only for the postgonorrheal complications involving the joints but also for polyarthritis associated with unspecific urethritis A similar relation to pelvospondylitis ossificans has also been documented in that a high incidence of prostatovesiculitis has been demonstrated in men with this disease first by Romanus (17) and later verified by several workers (Domeij et al (2) Mason (11) Oates (12) Olhagen (13) and others) We have noticed that since we started systematically to direct the treatment to the cure of the urological disease both our uro arthritis and our pelvospondylitis cases have run a much more favourable course in comparison with our earlier cases and with available published data We have therefore made a retrospective analysis of a group of patients with these diseases for the purpose of trying to objectify these impressions Since varying figures have been reported for the incidence of

cases in which Reiter's disease has developed into pelvospondylitis we also studied the relation between the two conditions.

The nomenclature used here may perhaps contribute further to the confusion in this field. Hollander was the first to suggest that the term "infective uro-arthritis" should replace the term Reiter's disease. Olhagen has reduced this designation to "uro-arthritis" which is used as a collective term for those rheumatic conditions that develop in association with urogenital infections. *The term thus includes not only acute and* chronic disorders, such as postgonorrheal arthritis and the complete Reiter's triad but also abortive forms of Reiter's disease, that is polyarthritis with urogenital infection alone, without conjunctivitis. Extra-articular equivalents, such as achillotendinitis and tendoperiostitis of the calcaneus, are also included under this term. One reason for the altered nomenclature is that after specific urethritis, that is gonorrhea, virtually the only syndromes seen nowadays are those which cannot be differentiated clinically from those appearing after unspecific urethritis and which, unlike the metastatic gonococcal arthritis, do not respond directly to penicillin. Another reason why we do not use the term Reiter's disease is that cases of postenteritic Reiter syndromes are not included in this study. In addition to the imperative sacroiliac joint changes, our criteria for a diagnosis of pelvospondylitis included evidence of spondylitis as defined by Romanus & Ydén (18).

MATERIAL

The study comprised the patients who had been admitted to the Rheumatological department of Karolinska sjukhuset since 1954 and who were resident in the Stockholm region. Out of 190 patients invited to join, 30 failed to appear in spite of repeated requests. Two-thirds of these were cases of acute uro-arthritis and one third were pelvospondylitis cases. Most of them had clinically improved or recovered at the last examination. 36 of the 160 followed up patients were for various reasons withdrawn from the analysis of the material. This means that patients with *psoriasis or other non-urological associated diseases*, such as ulcerative colitis and regional enteritis, were not included. Advanced cases of pelvospondylitis, in which complete "bamboo spine" was noted at the first examination, were also excluded, as one of the main objects of the study was to follow the development of the radiographic changes and this cannot be done after the joints have become ankylosed.

TABLE I

Clinical Features

		Uro arthritis	Sacroiliitis	Pelvospondylitis
Diagnosis				
Number of cases		71	4	49
Sex	Male	63	1	40
	Female	8	3	9
Type of onset		Per cent	Per cent	Per cent
	Acute (peripheral)	56 3	0	28 6
	Subacute (peripheral)	38 0	0	28 6
	Spinal	5 7	100	42 8
Peripheral joint involvement (some time)		100	0	85 7
Eye involvement	Conjunctivitis	21 1	0	8 2
	Iritis	18 3	0	34 6

The composition of the material will be seen in table I 71 of the patients had uro arthritis 49 had pelvospondylitis and 4 forming a special group had sacroiliitis alone 11 % of the uro arthritis group and 18 % of the pelvospondylitis group were women In no less than about half the spondylitis patients the disease started with peripheral symptoms and nearly 86 % of them had had such symptoms on some occasion as had all the uro arthritis patients According to general experience there is a higher incidence of conjunctivitis in uro arthritis patients as was also the case in our material where it was 21 % as against 8 % in the pelvospondylitis group while the incidence of iritis was higher in the pelvospondylitis group (34 6 % as against 18 3 %) The length of the observation period is shown in table II but the duration of illness was in most cases much longer (Table III) 33 patients had had their disease for more than 15 years

METHODS

The patients underwent *physical examination* special attention being paid to the condition of the spine and peripheral joints *Laboratory*

TABLE II

Follow up of Patients with Uro arthritis and Pelvospondylitis

Observation (years)	Number of patients Uro arthritis	Sacroiliitis	Pelvospondylitis
2—3	13		4
4—6	3	1	13
7—9	12	1	9
>9	23	—	23
Mean (years)	6 0	5 0	7 6

procedures included ordinary hematological analyses erythrocyte sedimentation reaction paper electrophoresis and measurement of antistreptolysin and antistaphylolysin titers Practically all the patients were examined by x ray of sacroiliac joints and spine at least twice and many were followed by repeated x ray examinations the last one being made in connection with the clinical follow up examination

X Ray Examination Pelvospondylitis is characterized radiologically by a certain periodicity showing periods of erosion followed by reparative phases in the form of calcification and ossification In the radiological assessment of the disease course with respect to progress we were therefore concerned only with the development of new erosive changes or evidence of healing reactions in areas in which the previous film had not shown such changes but in which the healing reaction indicated that they had been present

TABLE III

Follow up of Patients with Uro arthritis and Pelvospondylitis

Duration of Disease (years)	Number of Patients Uro-arthritis	Sacroiliitis	Pelvospondylitis
< 1	14		1
1— 5	6		5
5—10	16	4	16
10—15	5		6
>15	10		23
Mean (years)	8 1	8	16 6

In the *urological* assessment we followed the principles established by Domenj et al (2)

Therapeutic Regimen

In planning the treatment of the associated urological infection we usually consulted a urological specialist When pathogenic bacteria were present in the urine or in specimens from the prostate and vesicles or in urethral secretion antibiotics were given according to the result of the sensitivity test Patients in whom we found no bacteria but signs of previous infection in the form of positive gonococcal complement fixation test or increased antistreptolysin titer received penicillin To patients with increased antistaphylolysin titer alone or with negative serology but pus cells in the prostatic secretion we gave sulphonamides usually sulphadimethoxine (Madribon®) 0 5 g twice daily for 1 to 2 weeks and thereafter 0 5 g daily for months sometimes for years (The sulpha drugs were extremely well tolerated We noted only a few cases of hypersensitivity reactions and did not see any side effects in the form of blood disorders) Broad spectrum antibiotics especially tetracyclines were given to patients who did not respond to the sulpha drugs and occasionally to uro arthritis patients with acute urethritis Some patients with prostato-vesiculitis were given prostatic massage once weekly for some months though not if there was acute inflammation of the glands in view of the risk of exacerbation of any iritis or arthritis present

In other respects the treatment followed the current principles for active exercises For antiphlogistic therapy we used mainly phenylbutazone 200 mg daily in cases in which salicylates were not sufficiently effective (X ray to the spine was given in isolated cases of pelvospondylitis) Many patients with exudative synovitis received cortisone intraarticularly In exceptional cases we used short term systemic corticosteroid or ACTH treatment so as to be able to apply more intensive remedial exercise therapy

RESULTS

Clinically

The results recorded at the follow up examinations are shown in table IV and refer to such clinical parameters as subjective symptoms signs

TABLE IV

Status at Follow up

	Uro arthritis (71) + Sacroiliitis (4) (75)		Pelvospondylitis (49)	
	No	Per cent	No	Per cent
No residual symptoms Normal ESR neg serology	33	44	7	14 3
Ameliorated	32	4 7	24	49 0
Stationary	7	9 3	15	30 6
Worse	3	4	3	6 1

of activity in joint capsules and erythrocyte sedimentation rate About half the uro arthritis patients but only 14 % of the pelvospondylitis patients had recovered completely 43 % of the uro arthritis group and half the pelvospondylitis group showed marked improvement judged from reduced E S R and absence of joint exudate although subjective symptoms persisted All these patients were able to work In 9 % and 31 % respectively the condition was assessed as stationary and deterioration was noted in only 3 patients of each group Working capacity was radically reduced in only a few (Table V) Six patients had changed their occupation and 4 were drawing disability pensions 2 because of iritis and 1 because of depression and 1 had been granted a temporary pension on grounds of arthritis

It may be mentioned here that 73 % of the men with pelvospondylitis had initially shown signs of prostatovesiculitis in an active or inactive form At the follow up the prostatitis had healed in two thirds of the

TABLE V

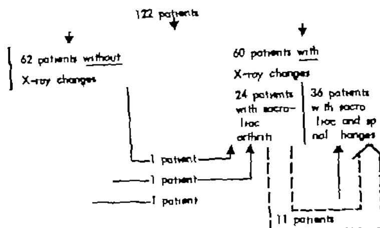
Radical Changes of Functional Capacity

	Uro-arthritis	Pelvospondylitis
New occupation	2	4
Invalid pension	2	

TABLE VI

X-ray Changes of the Spine

Initial status



Follow-up

59 patients without X-ray changes	63 patients with X-ray changes	
	15 patients with sacro-iliac arthritis	48 patients with sacro-iliac and spinal changes

cases Among the male patients with uro arthritis 47 (87 %) of 56 had had prostatitis which had cleared up

Radiologically

The radiographic follow up examination comprised all the 124 patients but data on the *initial* x ray are missing for 1 uro-arthritis and 1 pelvospondylitis patient and only 122 patients are therefore included in table VI 62 *uro arthritis patients* had primarily no radiological abnormalities in sacroiliac joints or vertebrae During the observation period which averaged 6 years radiological abnormalities of the spine developed in only 3 patients in 2 of them with involvement of the sacroiliac

TABLE VII

Follow-up of Radiological Changes of Pelvis and Spine in 48 Cases of Pelvospondylitis

	Stationary	New changes or progress of initial changes	
		Minor	Major
Sacroiliac joints	21	15	4
Lumbar spine	20	15	4
Dorsal spine	11	18	4
Cervical spine	1	7	

joints alone. Changes in sacroiliac joints as well as vertebrae developed in only 1 patient out of 62 (1.6 %). The mean observation period is short of course but the series includes patients who had had chronic uro-arthritis for 16 or 28 years without the development of any radiological changes in sacroiliac joints or vertebrae.

Out of the 24 patients who had sacroiliac joint changes alone at the first examination in the rheumatological clinic 11, or 46 %, developed signs of spondylitis later on. They were therefore classified as pelvospondylitis cases.

The results of the radiological analysis of the *pelvospondylitis cases* will be seen in table VII. We found that the disease had not progressed in 40 % of the cases and noted slight progress or minor fresh changes involving mainly the lower thoracic vertebrae in about the same proportion of cases. In 4 patients, or barely 10 %, the disease had progressed markedly during the observation period, which averaged 7 1/2 years.

The clinical and the radiological analyses were made independently of each other. A comparison of the results shows some discrepancy in that patients in whom there had been slight progress radiologically during the observation period were free from symptoms or showed improvement at the follow-up examination (Table VIII).

DISCUSSION

The investigation verifies earlier observations (4, 5, 6, 10, 17, 18), namely that acute uro-arthritis including both the complete Reiter's syndrome and abortive forms (without conjunctivitis) can develop into *sacro-*

TABLE VIII

Comparison between Clinical and Roentgenologic Parameters Pelvospondylitis

Roentgenologic status		Clinical status			
		No residual symptoms	Ameliorated	Stationary	Worse
Stationary	22	4	10	7	1
Minor progress	27	2	14	4	2
Major progress	4	1	—	3	—

iliac arthritis However in such patients with urethritis followed by acute peripheral joint symptoms the incidence of sacroiliac arthritis was 15 5 % during an observation period of 6 0 years (cf Mason s et al figure of 45 %) Signs of spondylitis developed in 12 of 48 patients during an observation period of 7 6 years i e in 25 % of the cases However in only 1 of these patients x ray changes of the spine were absent at the first examination the other 11 already had sacroiliac arthritis at the start of the treatment When looking at the natural history of the pelvospondylitis cases (Table I) it is apparent that not less than 57 2 % had a *peripheral* type of onset furthermore one third of the pelvospondylitis cases could be classified as acute uro arthritis from the beginning This implies that earlier (before we started our therapy regimen) a rather high percentage of uro arthritis cases developed into ankylosing spondylitis which is to be contrasted with 1 6 % in the present series But any information that can be derived from such figures is of limited value as much longer observation periods would be necessary perhaps 15 years at least

Although there is reason to believe that we are concerned with essentially the same disease the clinical patterns differ The typical pelvospondylitis often has an insidious onset and is attended with symptoms referable to the lumbosacral region whereas uro-arthritis is of more acute onset and involves peripheral joints preferentially the large joints of the lower extremities The urological symptoms are much more prominent in uro arthritis while for instance prostato vesiculitis in pelvospondylitis is often clinically quiescent only palpation microscopical analysis of expressed matter and needle biopsy will show unequivocal signs of an inflammatory reaction

Radiologically there was no difference between the findings in the

spine of patients with typical pelvospondylitis of spinal onset and those in patients in whom the disease started with peripheral joint symptoms that is uro-arthritis which had developed into pelvospondylitis

The investigation has verified the primary clinical impression that the prognosis with respect to working capacity is good in both conditions and apparently better than what was believed earlier In a leading article in Brit Med J 1966 (5) it is stated that though there are exceptions it seems probable that few patients who suffer from Reiter s disease make a complete or permanent recovery Our cases are what is more selected since patients with mild uro arthritis are not admitted to special clinics but are treated in military hospitals or departments of venereology Thus only 14 of our 71 followed up patients that is one fifth had had their disease for less than 1 year (To this number may be added 20 patients with acute arthritis who failed to attend the follow up examination and who had probably recovered) The follow up showed however that 44 % of the uro arthritis patients were completely free from symptoms and able to work at the time of the examination One comparable study of the same kind is that presented by Csonka in 1959 comprising 134 patients with Reiter s disease only 4 of whom made a complete recovery and 43 % were able to carry out light work (the slightly longer duration of illness in Csonka s patients can only partly explain the great difference in the long term results between our and his series) Good (6) followed up 47 patients with Reiter s syn drome and found that only 5 had recovered completely Out of our 71 uro arthritis patients only 2 were drawing a disability pension (because of iritis) the rest were all working 2 had had to change work Neither ankylosing peripheral joint changes nor foot deformities which are usu ally described as important disability reasons in chronic Reiter s disease had developed in any of them In our group of pelvospondylitis patients there was the same low figure for disability at the time of the follow up examination out of 49 patients 1 was granted a temporary disability pension because of his joint disease and 1 a disability pension on grounds of depression None developed a kyphosis For the sake of comparison it may be mentioned that Parry (15) examined a series of cases of pelvospondylitis in military personnel who had been treated with physical agents and antiphlogistics and by x ray Follow up examina tion of 170 patients after an average observation period of *6 years* showed a disability rate of 36 % Kyphosis had developed in 15 patients and was severe in 2

Why do our patients show so much better functional capacity than do the patients in earlier series? Obviously ethnic and climatic factors can play a part there are probably differences with respect to the social and financial conditions of the patients But the essential difference between earlier series and ours concerns the treatment Our patients were under consistent urological supervision and long term treatment with sulphonamides and/or antibiotics As we do not consider the possibility of omitting antibiotic therapy in cases in which a significant bacterial infection is present we cannot obtain a control series of our own and so prove the value of this part of the treatment, which is directed towards the infective component in the disease complex In prospective studies e g by Popert (16) in which the unspecific urethritis was treated with tetracyclines for five days the treatment was not found to have any influence on the course of acute Reiter attacks But of course such an effect is hardly to be expected if a comparison is made with penicillin treatment of streptococcal infection in rheumatic fever All experience shows that antibiotics do not influence the acute course of rheumatic fever but that they are extremely effective in preventing fresh streptococcal infections The situation is of course much more complicated as regards uro genital infections in which the etiology is as yet unknown, with the exception of postgonorrheal arthritis and in which various microbes are considered such as bacteria mycoplasmas virus (Chlamydia etc) In some cases, however there is bacteriological and/or serological evidence indicating that bacterial antigens are involved e g (Neisseria, staphylococci streptococci enterococci E coli) In other cases Mycoplasma has been found to be present in this clinic Jonsson (9) has demonstrated Mycoplasma in joint fluid from 6 patients with acute uro arthritis Others (7 12) have found serological evidence for Mycoplasma infection with positive antibody reactions in about 50 % of their cases A feature common to bacterial and Mycoplasma infections is that both are influenced and can be prevented by sulphonamides and/or antibiotics It is therefore conceivable that long term treatment with sulpha drugs or tetracyclines has had a prophylactic rather than a curative effect analogous with the preventive effect of penicillin against rheumatic fever

However it might well be that the tetracycline therapy which was administered in some cases has quite a different point of attack from that originally intended This drug in fact also changes the intestinal anaerobic flora Recent findings by Olhagen & Mansson (14) indicate

that chronic inflammatory connective tissue diseases especially rheumatoid arthritis but also many pelvospondylitis and sacroiliitis cases display an abnormal flora of Clostridium perfringens in the intestine as well as immunologic responses in the form of circulating and cell bound antibodies against clostridial alpha toxin Such changes have also been found in cases of Reiter s syndrome but more rarely The possible role of Clostridium perfringens in the pathogenesis of inflammatory joint diseases remains to be made clear however

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26 March 1970

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From the Second Medical University Clinic, Kiel
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Germany

DIFFERENTIATION OF INFLAMMATION AND OSSIFICATION IN SPONDYLARTHRITIS ANKYLOPOIETICA

By

U Langness D Banavsky J Alexopulos W Kriegel and R Burger

Summary In 50 patients with classic spondylarthritis ankylopoietica, the collagen like protein (CLP) the immune globulins, the SR and the $alpha_2$ globulin fraction besides clinical and x ray diagnostics were determined and compared with data from 40 normal persons Progressive spondylarthritis ankylopoietica was always correlated to an elevated CLP level in plasma Besides CLP in the cases of an active inflammatory rheumatic process, there was also an increase of the immune globulins, of the SR, and probably of the $alpha_2$-globulins If, on the other hand the activity is seen in the ossifying process only the CLP level was elevated The latter was correlated to the activity not to the extent of ossification as estimated by x ray In spite of the methods mentioned the states of some patients with simultaneous inflammation and ossification cannot be differentiated except by observing the clinical course Nevertheless a good method of differentiation has been created for many patients and thus the foundation of specific therapy has been laid

Spondylarthritis ankylopoietica attacks all joints of the spine the sacroiliac joints and the paravertebral connective tissue A combination with peripheral arthritis is found in nearly 10 % of the patients (5)

Spondylarthritis ankylopoietica is primarily an inflammatory disease it begins polycentrically and progresses continuously As a secondary trait ossification appears and proceeds autonomously even after the inflammation has stopped (3) Destruction sclerosis and ankylosis are identified by x ray (1)

The progression of the disease is clinically observable through the increase of pain and x ray alterations as well as by decrease of mobility It has been shown that progression can also be estimated by biochemical methods e g by determination of the serum level of collagen like protein (CLP) (8) The immune globulins in serum are of similar importance As will be shown, IgA and IgG are raised significantly in some cases in the active phase

The therapy depends on whether the inflammatory or ossification process predominates A differentiation based on clinical or x ray status cannot be made except after longtime observation As will be shown here the simultaneous consideration of laboratory data such as SR, serum electrophoresis especially immune globulins and collagen like protein allows the two courses to be differentiated more rapidly and with reasonable precision

PATIENTS AND METHODS

We examined 50 patients all of whom were definite cases of spondylarthritis ankylopoietica 43 males and 7 females, as well as 40 normal persons for comparison Most patients had only had physical therapy some had been given small doses of Indomethacin After the clinical course we separated cases with progressive spondylarthritis ankylopoietica from those with the stationary variety After estimation of clinical and x ray data we determined —

1 Collagen like protein (CLP) in plasma according to Le Roy & al (12)
2 Immune globulins (IgA IgM and IgG) according to Mancini (14)
3 SR according to Westergren
4 Alpha$_2$-globulin fraction by serum electrophoresis according to Grassmann and Hannig (4)
5 Serum glutamate oxalacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) in the optic kinetic test of Boehringer

TABLE I

Levels of Collagen-like Protein (CLP) in Plasma, Sedimentation Rates (SR) and Concentrations of Alpha Globulin Fractions in Serum in 33 Patients with Progression and 17 with Stationary Spondylarthritis Ankylopoetica as well as in 40 Normal Individuals

Group	n	CLP (µg/ml.) in plasma		ESR (mm.) 1st hour		Alpha₂ globulin fraction in serum (relative %)	
		6.5—13.2	>13.2	<10	>10	6—12	>12
Patients with progressive spondylarthritis ankylopoetica	33	2 (9.4)	31 (38.4±25.3)	14	19	21	1 (14.1±1.9)
Patients with stationary spondylarthritis ankylopoetica	17	14 (9.7±3.1)	3 (15.5)	17	Ø	17	Ø
Normal individuals	40	40 (8.7±2.4)	Ø	40	Ø	40	Ø

RESULTS

Status as regards SR, alpha$_2$ globulin fraction and CLP in serum is shown in table I. SR rose significantly in most cases of the progressive course of spondylarthritis ankylopoetica. In the stationary cases we found only normal values during the first hour. Not quite one third of the cases with a progressive course of the disease showed an increase of the alpha$_2$ globulin fraction; in stationary cases it was wholly within the normal range. The most pronounced feature was the difference of the CLP levels ($p < 0.001$). In only two patients out of 33 with a progressive clinical course the serum level was within the normal range. On the other hand, three patients out of 17 with a stationary course of the disease showed a slightly raised CLP level. A further significant difference between the two groups of the disease

TABLE II

Concent ation of Immunoglobulins IgA IgM and IgG in Serum in 33 Patients with Progressive and 17 with Stationary Spondylarthritis A kylopoetic as ell as 40 Normal Individuals

Group	n	IgA(mg%)	IgM(mg%)	IgG(mg%)
Patients with progressive spondylarthritis ankylopoetica	33	310±180[1]	178±90[4]	11 0±4?0[7]
Patients with stationary spondylarthritis ankylopoetica	17	280± 87[2]	180±87[5]	1 50±335
Normal individuals	40	175± 83[3]	170±85	1?00±?60[9]

1 2 p< 0 05	4 5 p> 0 05	7 8 p< 0 05
1 3 p< 0 001	4 6 p> 0 05	7 9 p< 0 01
2 3 p> 0 05	5 6 p> 0 05	8 9 p> 0 05

was recognizable in the IgA (p < 0 05) and IgG (p < 0 05) while the IgM was uncharacteristic (Table II)

Table I also reveals that certain progressive cases of the disease can

Collagen Like Protein (CLP) in Plasma (μg/ml)

50
40
30
20
10

++ +++ ++++ ++ +

Ossification Determined by X-Ray

Fig 1 Correlation of radiographically determined ossification to level of collagen like protein (CLP) in plasma

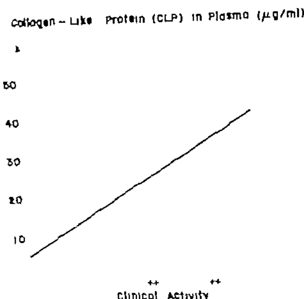


Fig Correlation of different stages of clinically determined activity to level of collagen like protein (CLP) in plasma in 14 patients with progressive spondyl arthritis ankylopoetica without definite signs of inflammatory activity ($y = 9\,4\ x + 6\,12\ r = 0\,576\ p < 0\,05$)

have normal SR but an increased CLP level From the total of 33 patients 14 had an SR below 10 mm but an increased CLP level The mean value $\pm$ 1 SD in this group was 31 5 $\pm$ 14 7 μg/ml In these cases the CLP level can only be seen in connection with the ossifying process In these 14 patients the immune globulins were within the normal range an indication — as in the case of the SR — that in such cases the inflammatory processes are unimportant Comparison of the CLP level with the extent and gravity of x ray alterations showed no correlation (Fig 1) It could be deduced that it is not the existing extent but the activity of the ossification which influences the CLP level in plasma (Fig 2)

In order to exclude the possibility that the immune globulin alterations mentioned above might have been caused by a damage to the liver we determined the SGOT and SGPT The serum level rose slightly in only a few cases but in these cases both clinical status and anamnesis had few data as regards a liver damage

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10 Feb 1970

Isomäki H & al Acta Rheum Scand 17 23—36 1971

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SPLENOMEGALY IN RHEUMATOID ARTHRITIS

By

H Isomäki* O Koivisto & K Kiviniitty

Summary The size of the spleen in 17 patients with active rheumatoid arthritis and of 12 control patients was determined by isotope scanning The average size of the spleen was 440 ± 220 cu cm for the rheumatoid patients and 250 ± 85 cu cm for the control patients The largest spleen in the control series was 395 cu cm and ten of the 17 patients with active RA had a larger spleen

It is known that about a quarter of the patients with juvenile rheumatoid arthritis (1) and 5—10 per cent of the adults with rheumatoid arthritis (6) have splenomegaly Felty's syndrome (2 3 4 6 8) is an extreme form of this condition in which splenomegaly of the arthritic patient is allied with leucopenia or thrombocytopenia Since information on the size of the spleen in patients with RA is based only on palpation and percussion findings and on a few operative findings the following study was carried out using isotope scanning to determine the size of the spleen

MATERIAL AND METHODS

The series comprised 17 outpatients at the Department of Medicine of Oulu University All had erosive peripheral RA in the active phase

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TABLE I

The Sex Age Latex Hemoglobin Leucocyte Count Platelet Count and Spleen Size of 17 Rheumatoid Patients

Patient	Sex	Age	Latex	Hb	Leuc	Thromboc thousands	Spleen size cu cm
NY	M	41	+	—	—	—	930
HJ	F	50	+	9 9	5 900	180	900
MM	F	48	+	11 7	8 500	286	680
HF	F	47	+	11 7	5 900	238	600
KH	M	46	+	14 2	11 000	195	550
EH	F	40	+	9 4	5 500	490	500
AH	F	39	+	9 9	6 500	—	480
PJ	F	16	+	—	—	—	440
AM	F	20	+	11 3	8 500	260	420
HK	F	40	+	10 9	3 500	320	470
BP	F	22	+	10 0	7 400	284	350
LS	F	59	+	11 1	7 700	190	260
LT	F	29	+	9 6	8 300	505	250
KA	F	32	+	12 3	10 400	320	270
JA	F	43	—	—	9 000	155	210
PE	F	51	+	11 4	6 500	180	210
LJ	F	61	+	—	—	—	190
Mean value							440

The control series consisted of 12 patients from the same Department hospitalized as well as outpatients None of the controls suffered from RA or any other collagen disease An effort was made to choose control patients with a complaint not known to be associated with splenomegaly

The scanning of the spleen was carried out using the patient s own red cells labelled with Hg^{197} Scanning was performed in two directions straight towards the front and straight towards the left flank The size of the spleen was calculated by approximation from the scanning results without it being known which of the patients had RA and which were controls

RESULTS

Tables I and II present the patients age sex and size of spleen In addition for patients with RA the hemoglobin blood leucocyte and

TABLE II

The Sex Age Spleen Size and Reason for Admission to Hospital of the 12 Control Patients

Patient	Sex	Age	Spleen size cu cm	Admitted to hospital for
ET	M	40	395	stenocardia
AK	M	34	380	observation
SS	F	4	280	observation
PK	F	51	260	observation
KB	M	47	235	stenocardia
AS	F	38	220	observation
SK	F	59	185	stenocardia
KA	F	46	180	observation
EH	F	61	175	cholelithiasis
AA	F	57	165	trauma
JI	F	50	150	observation
HA	M	31	140	trauma
Mean value			230	

platelet levels and the result of the Latex test are given The reasons for hospitalization of the control patients are listed

In patients with RA, the mean size of the spleen was 440 cu cm standard deviation 220 cu cm For the control patients the corresponding values were 230 and 85 cu cm respectively The difference is statistically significant

DISCUSSION

Fischer and Wolf (5) scanned the spleens of 500 healthy subjects The upper limit of the surface area of the spleen they obtained 70—80 sq cm agrees with the mean volume we obtained for the spleen of the control patients The control series therefore can be considered normal on this account

The largest spleen of the control series was 395 cu cm The spleen of ten out of the seventeen patients with active RA exceeded this volume From the measurement by isotope scanning it may be concluded that splenomegaly in rheumatoid patients is apparently more common

than has been realized Determination by clinical means of the size of a slightly enlarged or normal spleen is impossible

The spleen which on isotope scanning had proved to be enlarged could in a non rheumatoid series be detected by percussion and palpation in only about one third of the patients (5)

The patients with RA in the present series were all selected with the disease in the active phase The extent to which the size of the spleen depends on the activity of the RA the duration of the disease or e g the rheumatoid factor was not analysed in the present study

The finding that the enlargement of the spleen in patients with RA is more common than was earlier realized supports the view that Felty s syndrome should not be considered a separate disease but is rather an extreme form of ordinary RA in which the spleen is grossly enlarged Leucopenia thrombocytopenia and increased susceptibility to infection may be secondary symptoms accompanying the splenomegaly This is suggested by results which show that susceptibility to infection and leucopenia in patients with Felty s syndrome diminished after splenectomy (6 7 8)

The present series contained no patient who might be said to have Felty s syndrome even though in some cases the spleen was considerably enlarged Two patients had low leucocyte counts 3 500 and 3 990 per cu mm and they both had splenomegaly None of the patients had leg ulcers or increased susceptibility to infections

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We are very grateful to miss Kyllikki Nosa for giving valuable technical assistance

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6 April, 1970

Oka M Rekonen A & Ruots A Acta Rheum Scand 17 27—30 1971

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Tc 99m IN THE STUDY OF SYSTEMIC INFLAMMATORY ACTIVITY IN RHEUMATOID ARTHRITIS

A Preliminary Report

By

M Oka A Rekonen and A Ruotsi

Summary A method is presented for the estimation of systemic rheu matoid activity using Tc 99m uptake measurements above peripheral joint areas

Estimation of systemic inflammatory activity in rheumatoid arthritis (RA) continues to be a problem There are no generally accepted objec tive criteria for this purpose The evaluation of the activity of the disease has been far too highly dependent on the physician s experience or the patient s statements No single laboratory test correlates well enough with the systemic inflammatory activity in RA The figures used as measures of the activity of the disease have been based on formulas combining several clinical and laboratory data (1 2 3) However the methods have been crude or complicated with many sources of error and the scoring systems used by different workers have not been comparable to each other

The radioisotope technetium 99m (Tc 99m) has been used for the study of inflammatory activity in individual joints (4 5) Accumula tion of the isotope in an inflamed joint reflects enhanced circulation of the synovial membrane and other joint tissues A strong uptake is observed in joints that are severely inflamed and a lower uptake in those that are only mildly and moderately affected

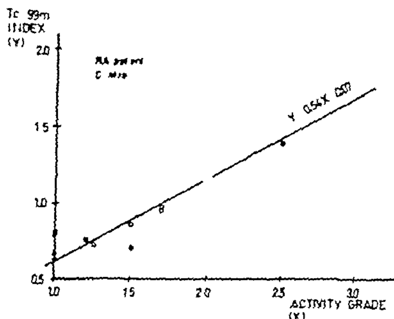


Fig 1 Correlation between the Tc 99m index and the disease activity grade (Duthie & al) in rheumatoid arthritis (o) and healthy controls ( )

The purpose of the present paper is to describe a method developed by us for the objective measurement of systemic inflammatory activity in RA Our preliminary data suggest that quantitative Tc 99m uptake measurements above joints can provide a reliable index of systemic disease activity For this it is essential that the Tc 99m uptake measurements cover a sufficiently large number of joints including those which are the most frequent sites of rheumatoid synovitis

METHOD

As sites for measurement we have chosen six joint areas 1 hands and wrists 2 knees 3 feet and ankles The procedure is as follows A dose of 0 5 mCi of Tc 99m is injected intravenously into the cubital vein The apparatus is a conventional iodine measuring system (Wallac, Turku Finland) The crystal skin distance is 37 5 cm and the diameter of the measuring field 20 cm Measurements are started 30 minutes after injection The duration of the measurement on each area is 30 seconds

In the hands and wrists the midpoint of the measuring field is half way between the knuckles and the wrist The patient s hands are clenched, the patient is seated and the measurement is made from the dorsum In the knees the measurement is performed in the anteroposterior projection with the collimator directed toward the center of the patella In the feet and ankles the measurement is made on the plantar side, the mid point halfway between the talocrural and 1st metatarsophalangeal joint In addition the radiation is measured in the anteroposterior projection above the heart and the urinary bladder (midpoint in the upper margin of the symphysis)

The rheumatoid activity index (Tc 99m index) is calculated by summing up the counts on the six joint areas and dividing the values so obtained by the mean of the counts on the heart and the bladder In five healthy controls the Tc 99m index ranged from 0 60 to 0 84 In the figure values are presented for a group of unselected RA patients in whom the Tc 99m indices are compared with the disease activity grades estimated in accordance with the scale of Duthie et al (1) In the latter method the disease activity is evaluated from the ESR Hb and clinical severity of the systemic and joint symptoms There is a highly significant correlation ($p < 0.001$) between Tc 99m index and Duthie s disease grade in this limited series

The crucial points in the reliability of the Tc 99m index are the time of measurement after the isotope injection and the total joint area to be counted A more detailed analysis of a larger series of RA patients studied with this method is now in progress In this series eight joint areas including the elbows are measured

An objective measure for rheumatoid inflammatory activity is of special value in drug trials and for following the course of the rheumatoid disease process The Tc 99m index seems to be promising for these purposes The method could also be used in multi center therapy trials Neither the quality of the measuring apparatus nor the experience of the examiner will influence the result

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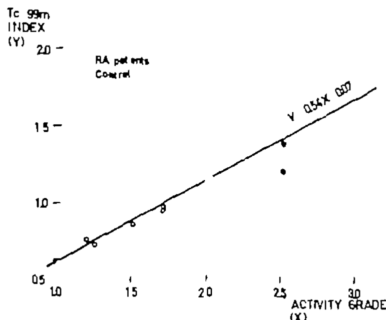


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ADJUVANT ARTHRITIS IN MICE AND HAMSTERS

By

W KETTEL R WILLE A FRANKE and J ZIEGELER

Summary Adjuvant arthritis has so far been observed only in rats It was attempted successfully to induce this disease in mice and hamsters The incidence of arthritis was 28 per cent In comparison to the disease in rats the course tended to be milder and biphasic, the symptoms on the front paws were relatively severe The period of latency and the histological picture resembled those in rats It is concluded that adjuvant arthritis is a non species-specific form of delayed hypersensitivity reaction the antigen of which is as yet unknown

Adjuvant arthritis begins 12—19 days after a single intradermal injection of Freund's complete adjuvant and thereafter manifests as polyarthritis various mucocutaneous lesions and iridocyclitis The evidence so far presented suggests strongly that this disease is an immunological process which might be produced by a hypersensitivity reaction of the delayed type to antigenic constituents of the injected mycobacteria (1 8 9) or to altered tissue at sites of injection (7) Adjuvant arthritis has so far only been provoked in rats Experiments by Pearson *et al* (6) and Lacapere (5) to produce this disease in dogs rabbits guinea pigs and mice have failed As there are some similarities between adjuvant arthritis and rheumatoid arthritis in man the question seems important whether the former is a species specific phenomenon or represents a

This work was supported by grants from the Arbeits und Forschungsgemeinschaft Rheumatologie Jena

TABLE I

Incidence Severity and Duration of Adjuvant Arthritis in Mice and Hamsters

No and species of animals	Site of injection	Conc of mycobact (mg per ml)	No of animals with arthritis	Arthrogram score*	Mean duration of arthritis (days)
20 Mouse	Ear	10	4	9	3
10 Mouse	Foot pad	10	4	39	9
10 Mouse	Tail	1	0	0	—
20 Mouse	Tail	10	5	6	2
10 Mouse	Tail	20		4	2
10 Hamster	Ear	10		31	5
10 Hamster	Tail	1	2	7	3
10 Hamster	Tail	10	3	15	2
10 Hamster	Tail	20	9	172	12

*Total of 11 evaluations

more general type of reaction It appeared to us that a re examination of the investigations mentioned might provide evidence for adjuvant induced joint lesions in other laboratory animals

METHOD

Seventy female mice of the Agnes Blum strain (6 weeks old and 20—30 g in weight) and forty hamsters (Mesocricetus auratus) of both sexes (12 weeks old and 60—100 g in weight) were injected intradermally at different sites with 0 1 ml of complete Freund's adjuvant The adjuvant contained 1—20 mg heat dried M tuberculosis in 1 ml paraffin oil The sites of injection and the concentration of tubercle bacilli in all groups are listed in table I The animals were examined daily during 28 days Joint involvement was evaluated by the visible swelling of the joints with the aid of an arthrogram score from 0 — 3 (2)

RESULTS

The most important results are given in table I As can be seen 15 of 70 mice and 16 of 40 hamsters i e 28 per cent of the animals devel

oped arthritis The onset of joint symptoms was observed between the 13th and the 26th day after the injection of the adjuvant In the hamster groups there was a significant increase in the number of arthritic animals and the severity of disease with higher concentrations of mycobacteria in oil ($p < 0.05$ if the groups with 1 — 10 mg mycobacteria were compared with those of 20 mg) The site of injection was of minor influence on the incidence and severity of the disease In hamsters a biphasic course of arthritis was apparent The first maximum was recorded on the 16th the second on the 22nd day after injection Unlike adjuvant arthritis in rats (4) there was in hamsters a more severe joint inflammation of the front paws even when the animals had been injected in the tail The arthrogram score of the front paws was 190 that of the hind paws 54

One animal of each species showing joint involvement was killed on the 14th and on the 21st day after injection of the adjuvant The joints were studied histologically As in adjuvant arthritis of rats suppurative arthritis and periarthritis had developed in mice and hamsters

DISCUSSION

According to our study the development of arthritis after intradermal injection of Freund's complete adjuvant is not restricted to rats If pain is taken to mix the constituents of the adjuvant thoroughly and to inject the adjuvant strictly intradermally similar lesions will occur in other species too The arthritis in mice and hamsters resembles that in rats by time of onset and a similar clinical and morphological picture It differs from the disease in rats by its milder and biphasic course lower incidence of joint symptoms and the preference of the front paws to be affected mainly in hamsters

Unpublished data (4) show that the injection of adjuvant in man is followed by edema of the fingers and painful swelling of the proximal interphalangeal and metacarpophalangeal joints Therefore it might be assumed that the adjuvant arthritis is a common reaction with some species specific differences of its clinical course and that in all species this disease depends basically on the same mechanisms The exact nature of this reaction and the relationship between adjuvant arthritis and rheumatoid arthritis in man remains unknown

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10 Mouse	Tail	20	2	4	2
10 Hamster	Ear	10	2	31	5
10 Hamster	Tail	1	2	7	3
10 Hamster	Tail	10	3	13	2
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Abe T & Homma M Acta Rheum Scand 17 35—46 1971

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IMMUNOLOGICAL REACTIVITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Humoral Antibody and Cellular Immune Responses

By

TOHRU ABE and MITSUO HOMMA

Summary Immunization with tetanus toxoid as humoral antibody formation and skin tests with DNCB PPD and macrophage response as delayed cellular immune response have been performed in twenty patients with systemic lupus erythematosus (SLE) as well as in twenty controls matched for age and sex.

No difference was found between the SLE group and the control group with respect to the frequency and intensity of positive reaction to tetanus toxoid while significant hyporeactivity to DNCB PPD and macrophage response was found in SLE. This cutaneous hyporeactivity could not be correlated with presence of clinical activity titer of antinuclear factors in serum and dosage of prednisolone

Great increase in our knowledge of immunology in the past few years has recognized that certain human diseases are associated with malfunction of the *immune system* Systemic lupus erythematosus is one of these disease conditions (21) and is generally considered to represent an auto immune disease The sera of patients with SLE are capable of giving positive serological reactions with cell nuclei (18) nucleoprotein (20) DNA (12 8) cytoplasmic component (39) thrombotic and clotting factors (22) These immune reactions are not primarily responsible for the disease process and the impression has arisen therefore that SLE patients are abnormal antibody producers

Results of humoral antibody response to foreign antigen in patients with SLE have yielded conflicting results (4 43) Stevens has demonstrated vigorous response to Vi antigen in SLE (37) Baum demonstrated hyporeactivity to brucella antigen (4)

As to delayed type hypersensitivity Friedman Bardawil Merril and Hanau (14) observed a 24 hour delayed type cutaneous hypersensitivity to homologous and autologous leucocytes in 16 of 20 patients with SLE (14) Bennett and Holley (5) tested six SLE patients with intradermal calf thymus DNA and obtained negative results Chieregato and Pardarini (10) also reported negative calf thymus DNA skin test in five SLE patients while Ores and Lange (33) reported a calf thymus DNA skin test with which they obtained a positive response at 24 hours in all of 19 SLE patients Azoury et al (2) reported that intradermal test using homologous leucocytes calf thymus nucleoprotein and calf thymus DNA was positive with different percentage and positive reaction to intradermal calf thymus DNA correlated with the presence of active SLE

The purpose of this paper was to describe immunological reactivities following immunization with tetanus toxoid as humoral antibody and DNCB PPD skin test macrophage response as delayed cellular response

MATERIALS AND METHODS

A *Patients*

Twenty patients with SLE were studied as also the same number of healthy controls matched for age and sex The diagnosis of definite SLE was made on the basis of predetermined criteria These were involvement of at least three of the organ systems usually affected in SLE laboratory confirmation by repeated findings of antinuclear and anti DNA antibody or typical renal lesion and exclusion of other diseases Clinically SLE was considered active by the presence of objective signs of inflammation in one or more tissue sites Polyarthritis active skin lesions and serositis were the dominant manifestations The criteria of lupus nephritis were persistent proteinuria with telescoping sediments and decreased renal function tests Pertinent data on each patient with SLE are summarized in table I Eleven patients had renal damage with variable activity At immunization the average dose of corticosteroid (prednisolone) was 10 9 mg (range 0—50 mg) and ten patients received no steroid

Patient No.	Age Sex	Arthr	Skin rash	Nephritis	D 1)	ANF 2)	LE cell	PSL (mg) 3)
1	1 M			+	2	16		0
2	6 F			+	16	16		20
3	19 F				32	256		10
4	21 F			+		6		0
5	22 M					32		0
6	23 F				2	16		0
7	2 F				8	64		0
8	25 F				3	256	+	5
9	26 F				2	256		5
10	27 F		+			64		0
11	28 F				8	16	+	30
12	29 F				2	8	−	0
13	30 M				6	256		5
14	30 F				2	16		0
15	31 F				2	16	−	4
16	33 F				6	32		10
17	35 F				2	256		5
18	38 F			+	16	16	+	15
19	42 F				2	8		0
20	45 F				4	32		0

1) anti-DNA antibody
2) antinuclear antibody
3) prednisolon mg q d

Table 1 Clinical and Serological Features

B *Serum Factors*

Before the tests venous blood was obtained from all patients and controls for determination of antinuclear antibody and anti DNA antibody titer Antinuclear antibody was determined by the immunofluorescent technique with rat liver section as the source of antigen and anti DNA antibody by spot test (9 19)

C *Immunization with Tetanus Toxoid**

1 Immunization of previously unimmunized persons Each person received two intramuscular injections of 0 5 ml of the same batch of tetanus toxoid at four week intervals Blood was taken for estimation of antitoxin at the time of each injection and exactly five weeks after the second injection

2 Re immunization Re immunization was performed six months after complete previous immunization with a dose of 0 5 ml of toxoid

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* Takeda Chemical Industries Osaka Japan Lot no H 23

D *Urine Preparation*

Twenty four hours urine was collected in plastic bottles containing 1 g of thymol as a preservative Protein concentration was determined by the Buret method on TCA precipitate with aliquot of urine The rest of the urine was concentrated by ultrafiltration and lyophilization, and then dissolved into normal saline with a final concentration of 6—7 g per 100 ml

E *Tetanus Antitoxin Titration*

It was performed in mice by the method described by Murata, Wada and Kubota (29) using serum and urine samples

F *Skin Tests*

1 DNCB* sensitization A sensitizing dose of DNCB (dinitro chlorobenzene) was applied to the circular area of skin 0 8 mm in diameter on the volar surface of the forearm by filter paper patch soaked with 0 1 m of 10 % DNCB in acetone The filter paper was removed after 24 hours The skin usually became erythematous within 2—3 days In one or two weeks the reaction had settled The presence of DNCB sensitization was tested three weeks later by application of filter paper patch with 0 1 ml of a 0 1 % solution of DNCB to the opposite forearm in the same manner The test was read after 72 hours In most of the normal individuals the lesion was raised about 0 5 mm above the surrounding skin and there was marked underlying induration (positive reaction) In some patients there was erythema but no induration (negative reaction)

2 Intermediate strength PPD** (0 0001 mg per 0 1 ml) 0 1 ml of antigen was injected intradermally in the volar surface of the forearm Reaction was read at 24 and 48 hours Millimeters of erythema and induration were recorded The test was considered positive when 5 mm or more of induration were present

3 Macrophage response A modified Rebuck and Crawley test (34) was used After cleaning the skin with alcohol an area of skin on the forearm 0 5 cm in diameter was lightly abraded with sterilized sand

* Daiichi Kagaku Co Tokyo Japan
** Takeda Chemical Industries Osaka Japan Lot no p 1 014

Category	No of Persons c̄ Tetanus Antitoxin u/ml								Total
	001	001	003	01	03	1	3	10	
Healthy Control	1	1	5	7	4	2			20
SLE	6	2	5	4	3				20

statistical significance of control vs SLE NS(p>001)

Table 2 Tetanus Antitoxin Response of Previously Unimmunized Persons 5 Weeks after The Second of Two Injections of Tetanus Toxoid

paper until fine reddish points appeared The lesion was covered with a glass cover slip After three hours the cover slip was removed and another was placed on the same lesion The process was repeated ad seriatum at 6 4 45 and 48 hours The cover slips were air dried and stained with Wright Giemsa stain and cells were counted

G *Statistical Analysis*

Statistical significance was based on x^2 analysis using Yates correction P values less than 0 01 by the chi square test were considered to be of statistical significance

RESULTS

Immunization with Tetanus Toxoid

A Response of previously unimmunized persons No detectable antitoxin was present in the sera taken from these subjects at the time of the first inoculation Table II indicates the tetanus antitoxin titers found five weeks after the second inoculation The antitoxin levels obtained from patients with SLE were rather comparable with those of the control group in most of the cases Although the number of subjects studied was admittedly small the absence of poor responders in the control group contrasts with the results in the SLE group The difference however between patients with SLE and matched controls was not statistically significant at the one percent levels of probability Analysis of

Patients No	Age	Sex	serum γ globulin (g/ of TP)	IgG (/ of TP)	% /24hr	Antitoxin serum	Antitoxin urine	PSL	Activity
1	15	M	185 /	39 %	075 g	<001	03	0	–
4	21	F	218	22	08	<001	01	0	
8	25	F	265	16	10	<001	<001	5 mg	–
11	28	F	275	92	08	<001	<001	30	+
13	30	M	345	12	13	<001	01	5	+
18	38	F	235	86	04	<001	<001	15	+

1) prednisolone mg q d
2) clinical activity a defined in the te t

Table 3 Urinary Excretion of Antitoxin in Poor Responder

six poor responders disclosed that all were patients with lupus nephritis This raises the question whether they may not really be poor responders but that normally produced antitoxin is partly lost into the urine

Table III indicates clinical data and antitoxin response of the poor responders Antitoxin was detected in urine samples from half of the poor responders (patients nos 1 4 and 13) which is indicative of a possible excretion of antitoxin into the urine

B Response to re immunization Table IV shows tetanus toxoid response to re immunization after six months Since the subjects studied had the same interval from the last inoculation and number and size of

Category	No of Persons ē Tetanus Antitoxin (Au/ml) <001	001	003-	01	03	1-	3	10	Total
Healthy Control				2	4	2	8	4	20
SLE		1	3	4	5	–	2	1	20

statistical significance of control vs SLE NS(p>001)

Table 4 Tetanus Antitoxin Response of Previously Immunized Persons

Category	No of pts M	F	Total	Age mean range	Reaction to DNCB Pos	Neg
Healthy Control	3	17	20	28 (15-45)	16	4
S L E	3	17	20	28 (15 45)	7	13

Table 5 Delayed Hypersensitivity Reaction to DNCB

boosting dose the results could be compared on the same basis Table IV shows that there was little if any difference in the capacity of SLE patients and matched controls to respond to one boosting dose But the difference between the two groups is not significant at the one per cent levels of probability

C Clinical features of SLE and antibody titer Clinically the disease was considered active in seven patients The degree of antibody response could not be correlated with any specific clinical or serological feature of the disease Antibody response of poor responders seems rather equal to the other patients if the titer was corrected for loss into urine

Skin Test

A Skin test to DNCB The result of DNCB is shown in table V Positive reaction occurred in 35 % of patients with SLE while 80 % of matched controls were positive This indicates some possibility of unresponsiveness to DNCB in some of the SLE patients

B Intermediate PPD (Table VI) Four of the twenty patients with SLE showed positive response to intermediate strength PPD while three quarters of the matched controls had a positive test This difference between SLE patients and matched controls is statistically significant When the response to DNCB and PPD was compared in individual subjects it was found that there was no tendency for the results to be concordant This significant lack of reactivity to tuberculin could not be explained on the basis of the exposure difference because SLE and control subjects should have had the same chance to be exposed

Category	Positive DNCB test	Positive Tuberculin test	Macrophage response>50% at 24 hr
Healthy Control	16/20 80	15/20 75	19/20 95%
SLE	7/20 35	4/20 20	2/20 10%

Table 6 Comparative Frequency of Individual with

C Macrophage response (Table VI) Only two of twenty patients with SLE reacted with macrophage response to more than 50 % while 19 of twenty controls reacted

Only one (5 %) of the SLE patients reacted to three skin tests

D Clinical and laboratory features of SLE and cutaneous reactivity (Table VII) *The patients ranged from 15 to 45 years of age*, three were males Clinically the disease was active in seven At the time of this study all patients had antinuclear factors in various titers Ten patients had not received prednisolone therapy Only one was receiving prednisolone in excess of 25 mg daily

Cutaneous reactivity could not be correlated with presence of clinical reactivity titer of antinuclear factors in serum or dosage of prednisolone Furthermore there was no obvious correlation between cutaneous reactivities and antitoxin response to tetanus toxoid

DISCUSSION

Systemic lupus erythematosus is generally considered to be the disease of an immunological aberration Many reports have been published to describe humoral (7 28 30 45) and delayed type sensitivity with different antigens (25 40 41 42, 44)

We used tetanus toxoid for the determination of humoral antibody response Tetanus toxoid was chosen because accurate and well estab

Patient No	Age	Sex	Activity	ANF	PSL	Skin Reactivity: DNCB	Tub. test	Macrophage
1	15	M	−	16	0	−	−	−
2	18	F	+	16	30	−	+	−
3	19	F	+	[illegible]	10	−	−	−
4	21	F	−	64	0	+	−	−
5	27	M	−	32	0	−	−	−
6	21	F	−	16	0	−	−	−
7	24	F	−	64	0	+	+	+
8	25	F	+	256	5	−	−	−
9	26	F	−	256	5	−	−	−
10	2	F	−	64	0	+	−	−
11	28	F	+	16	30	−	−	−
12	29	F	−	8	0	−	−	−
13	30	M	+	256	5	+	+	−
14	30	F	−	16	0	−	−	−
15	31	F	−	16	4	−	−	−
16	33	F	+	32	10	+	−	−
17	35	F	−	256	5	−	+	−
18	38	F	+	16	15	+	−	+
19	42	F	−	8	0	−	−	−
20	45	F	−	32	0	+	−	−

1) cl. clinical activity as defined in the text
2) anti nuclear anti body
3) prednisolone mg q.d.
4) tuberculin reaction
5) macrophage response

Table 7 Clinical Serological Features and Skin Reactivity

lished techniques are available for assessing antibody response and be cause man does not naturally have circulating antitoxin Most reports on immunization with tetanus toxoid (35 46) failed to show enhanced response Although there are reports that patients with SLE *responded* vigorously to brucella some blood types and antibiotics (17 28) our observation failed to confirm enhanced immunological response to tet anus toxoid Although there *is* no statistical difference in antibody formation between SLE patients and matched controls it is true that in this patient group there are poor responders Since the analysis of clinical data of these poor responders revealed that these are patients with lupus nephritis of *varying* activity loss of tetanus antitoxin into urine was thought a possible explanation of *poor response* (3 27 38)

As far as humoral antibody formation is concerned patients with SLE could be considered to be normal responders Therefore the possibility

of immunological aberration in delayed hypersensitivity is considered.

It was rather surprising that SLE patients showed hyporesponsiveness to DNCB, PPD and macrophage responses. Hyporesponsiveness to PPD is also described by Block et al. (6). The cause of the delayed skin test anergy in SLE is unknown but a few possibilities could be considered.

First, the skin unresponsiveness is the result of end organ failure (13), but this is not likely in the case of SLE patients.

Secondly, cachexia could be the cause. It is true that the delayed skin test response may be depressed in extreme cachexia and critical illness, but the patients studied are not in that category.

Thirdly, it has been proposed that there is a general defect in immunity in SLE, perhaps related to destruction of the reticulo-endothelial system by the disease. We know of no convincing evidence that RES is really destroyed in SLE (11).

Fourthly, it could be that patients with SLE circulate the lymphocytes of central lymphoid origin, which property would be relatively unresponsive to mitogens and unable to participate in delayed hypersensitivity reactions. In other words, varying populations of lymphocytes with different tissue origin and different functional properties may be present in the peripheral blood at the same time (16). Thymus, which is the apparent factor in autoimmunity, is known to be of the central lymphoid tissue, and thymic changes in SLE have been studied for their possible role in the pathogenesis of SLE (15, 24, 26).

Lastly, the therapeutic modality of corticosteroids may have some effect on unresponsiveness (23, 32, 36).

At the moment the cause of the unresponsiveness is not clear. We can only conclude that some as yet unidentified defect in the manifestation of certain cellular immune reaction is associated with SLE.

From this aspect, reports of association or development of so-called immunoproliferative disorders in SLE are challenging (1, 31). Further analysis of immunological reactivity in patients with SLE might be used for another approach to the study of the pathogenesis of this complex disease condition.

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ACID PHOSPHATASE ACTIVITY IN THE SYNOVIAL FLUID OF PATIENTS WITH RHEUMATOID ARTHRITIS AND OTHER JOINT DISORDERS

By

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Summary The acid phosphatase activity was examined in the synovial fluid of a series of 135 patients with different joint disorders. Enzyme assay and electrophoretic examination on starch gel were performed with alpha naphthyl phosphate as substrate. Patients with rheumatoid arthritis showed significantly higher levels than those with bacterial arthritis, osteoarthritis and non inflammatory joint effusions About 70 per cent of the patients with RA had higher acid phosphatase activities than those found among the patients with non rheumatoid diseases. Patients with chronic synovitis were found to represent a heterogeneous group, where those with low acid phosphatase activity recovered while those with a high activity frequently developed rheumatoid arthritis. Patients with bacterial arthritis had low acid phosphatase levels The results indicate that determinations of the acid phosphatase activity in the synovial fluid may be valuable in the diagnosis of RA and in the prognosis of other joint effusions

It has been suggested that lysosomal enzymes may play a destructive role in the damage of cartilage (7 8) A number of investigators have studied the activity of lysosomal enzymes in joint fluids and synovial tissue of patients with rheumatoid arthritis (RA) with the aim of elucidating the sequence of biochemical alterations which lead to joint deformities

TABLE I

Acid Phosphatase Activity in the Synovial Fluid of Patients with Different Joint Disorders

Activity expressed in micromoles of alpha naphthyl phosphate hydrolyzed per ml fluid per h

Patient group	Acid phosphatase activity M ± S E	S D	No examined
1 Classical and definite RA	2 86 ± 0 20	1 68	101
2 Probable RA	1 90 ± 0 73	1 91	7
3 Chronic monarticular synovitis	2 04 ± 0 51	1 66	10
4 Osteoarthritis with inflammatory complication	0 66 ± 0 20	0 49	7
5 Osteoarthritis	0 28 ± 0 08	0 23	9
6 Non inflammatory joint effusions	0 22 ± 0 05	0 09	17
7 Bacterial arthritis	0 20 ± 0 05	0 09	4

RESULTS

Quantitative Measurements of Acid Phosphatase Activity

The acid phosphatase activity in the synovial fluids of adult patients with different joint disorders is shown in table I The 108 patients with the diagnosis RA were classified according to the criteria of the ARA (14) Cases classifiable as possible RA were included in group 3 (Chronic monarticular synovitis) below

Groups 1 and 2 (Rheumatoid arthritis)

These patients showed clinical pictures of the disease in all stages of activity and with durations varying between one and fifty years

Among the patients in group 1 there were 12 cases with negative serological reactions at the time of the enzyme analysis The acid phosphatase activity was high also *in this group* (3 91 ± 0 86) and there was no significant difference from the seropositive rheumatoid patients

In group 1 four patients are included who had psoriasis Two of them had high acid phosphatase activity and a positive serological reaction for RA and the other two had low enzyme values and negative serological reactions

Four patients who had been subjected to synovectomy 4—8 months before enzyme analysis showed the lowest levels (0 25—0 49 micro moles/ml) in group 1 They had improved clinically and showed no signs of active synovitis in the operated joint

Group 3 (Chronic monarticular synovitis)

Ten patients with a chronic joint effusion confined to one knee joint at the time of enzyme analysis and with an observed duration of more than three weeks are included in this group All had a high sedimentation rate and a negative serological reaction for RA at the time of acid phosphatase determination Culture of the synovial fluid revealed no viral or bacterial growth X ray examinations revealed no bone destruction

Clinically all patients had signs of synovitis with palpable thickening of the synovial and periarticular tissues The etiology of the disease at the time of examination was unknown The average acid phosphatase activity was high and there was no statistically significant difference between this group and groups 1 and 2 The individual acid phosphatase values were quite variable however Three patients with activity values in the range of the non inflammatory groups recovered and after more than one year of follow up they exhibited no further signs of joint involvement Three other patients had moderately elevated acid phosphatase values The joints of two of them had been subjected to synovectomy recently The microscopic diagnosis was active nonspecific synovitis The third patient still had minor monarticular joint effusion after eight months In all three cases the definite diagnosis is unknown

The four patients with the highest acid phosphatase activities within one year developed a clinical picture characteristic of RA with polyarticular engagements and positive serological reactions

Groups 4 5 and 6 (Osteoarthritis and non inflammatory joint effusions)

In group 4 four patients were operated on with arthrodesis of the knee joint At operation all of them exhibited a picture of extensive synovitis Patient group 6 (non inflammatory joint effusions) included conditions as chondromatosis osteochondritis and meniscal injuries The difference between patients with RA (groups 1 and 2) and those with osteoarthritis and non inflammatory joint effusions (groups 4—6) is statistically highly significant ($P < 0.001$)

TABLE II

Relation between Total White Cell Count and Acid Phosphatase Activity in the Synovial Fluid of Patients with RA

Total white cell count	Activity M ± S E	No examined
>5000	2 44 ± 0 82	6
1000—5000	2 63 ± 0 68	9
<1000	2.21 ± 0.27	7

Group 7 (Bacterial arthritis)

Cultures established from synovial fluid at the time of enzyme analysis revealed growth of Staphylococcus aureus in two of the four cases In the other two cases Staphylococcus aureus was found in an earlier stage of the disease The samples of synovial fluid were obtained 4, 5 10 and 28 days respectively after onset All patients had sedimentation rates above 90 mm/h and clinical signs of acute inflammatory joint involvement

Relation between Acid Phosphatase Level and Total White Cell Count

No clear correlation was found between the total white cell count in the synovial fluids and the acid phosphatase activity (Table II)

TABLE III

Frequency of Detectable Acid Phosphatase Isozymes A and B in the Synovial Fluids of Patients with Different Joint Disorders

Patient group	No of patients with detectable A and B isozymes No	%	No examined
1 Classical and definite RA	90	89	101
2 Probable RA	3	43	7
3 Chronic monarticular synovitis	6	60	10
4 Osteoarthritis with inflammatory complication	1	14	7
5 Osteoarthritis	0	0	9
6 Non inflammatory joint effusions	0	0	17
7 Bacterial arthritis	0	0	4





Fig 1 Starch gel electrophoresis stained for acid phosphatase activity showing one sample of synovial fluid with no detectable activity (no 1) and another sample (no 2) with the typical 2 strongly staining enzyme components A and B + = anode

Acid Phosphatase Isozymes

The examination of whole synovial fluids by starch gel electrophoresis revealed two zones of acid phosphatase activity (Fig 1) in a high proportion of synovial fluids from patients with rheumatoid arthritis and chronic synovitis (Table III) In the synovial fluids of the patients with osteoarthritis non inflammatory joint effusions and bacterial arthritis no such enzyme zones were observed Samples of synovial fluid with high acid phosphatase levels in the quantitative

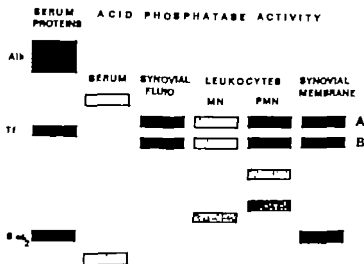


Fig 2 Schematic representation of the acid phosphatase isozymes in serum synovial fluid leukocytes and synovial membrane The electrophoretic positions of the A and B isozymes are indicated to the right To the left the mobilities of three major serum proteins are indicated Alb = albumin Tf = transferrin and $S\alpha_2$ = slow alpha macroglobulin The arrow points toward the anode

) measurements showed more strongly staining enzyme zones after starch gel electrophoresis The border of visibility on starch gel electrophoresis appears to be around the activity of 1 micromole per ml per h

The electrophoretic patterns for acid phosphatase under the same conditions as in the present investigation have been described in extracts of synovial membrane (3) and in most human organs (2) serum (5) and mononuclear and polymorphonuclear leukocytes (4) The electrophoretic patterns of serum synovial fluid leukocytes and synovial membrane were compared (Fig 2) The electrophoretic mobilities of the A and B isozymes were different from those of the two weak serum isozymes but corresponded to isozyme components found in both leukocytes and synovial tissue

DISCUSSION

The present investigation confirms previous results concerning an increase of acid phosphatase activity in the synovial fluid of patients

with RA In the investigation by Lehman et al (11) individulas with definite RA showed a fourfold increase on the average compared to patients with meniscal injuries In the present study the average activity among rheumatoid patients was thirteen times higher than that of patients with non inflammatory joint disorders Enzyme activity in the fluids from about seventy per cent of the rheumatoid patients exceeded the level of 1 0 micromole per ml which in this study represents the upper activity limit found in the patients with non rheumatoid diseases For screening purposes it would also be possible to apply the starch gel electrophoresis technique which has the advantage that 25 samples can be examined simultaneously on the same starch gel A finding of the two typical isozymes A and B in the synovial fluid indicates an acid phosphatase level exceeding the upper limit found in non inflammatory joint disorders

In contrast to other investigations the zymogram analysis and the enzyme assay were performed with the same substrate The substrate used in this study (alpha naphtyl phosphate) is not hydrolyzed by red cell acid phosphatase (9) In joint diseases the aspirated synovial fluids are frequently hemolyzed This background of erythrocyte acid phosphatase will not interfere in the technique used by us

It is remarkable that all four patients with bacterial arthritis showed very low acid phosphatase levels This series is small and therefore it is desirable to collect a larger series of patients with bacterial arthritis in order to confirm these findings

The group classified as chronic monarticular synovitis is of special clinical interest This category is apparently heterogeneous and composed of patients who may recover and those who may be developing RA which in fact we have observed These observations suggest that determinations of acid phosphatase activity in questionable cases may be of diagnostic and prognostic value

The observation that the increase of acid phosphatase in the synovial fluid of rheumatoid patients is due to two distinct isozymes (A and B) could be of help in the tracing of the origin of the raised enzyme activity in the synovial fluid Unfortunately components with the same mobility as acid phosphatase A and B occur in many different tissues (2) A serum origin seems excluded since the isozymes of acid phosphatase found in serum have electrophoretic mobilities different from those of the synovial fluid The two most likely sources are the synovial membrane and the granulocytes The A and B zones were found in

extracts of both the synovial membrane and granulocytes hence the analysis of isozymes cannot provide any critical information as to the origin of the increased acid phosphatase level in RA The weak correlation between total white cell counts and the acid phosphatase levels in whole fluids indicates that the acid phosphatase level is not primarily dependent on the *number* of white cells In agreement with our observations Yoshinari (18) found that the synovial acid phosphatase activity was dependent not only on the number of white cells in the fluid but also on the specific acid phosphatase activity of these cells It is also evident that besides the white cells also those of the synovial membrane (3 12 16) may contribute to the acid phosphatase activity of the whole fluids

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THE ANALGETIC ACTION OF DIMETHYL SULFOXIDE (DMSO) OINTMENT IN ARTHROSIS

A Double Blind Study

By

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Summary The analgetic action of 50 % DMSO ointment and placebo ointment was studied in patients with arthrosis by the double blind method A total of 100 treatment experiments of one month each were carried out. Favourable results were obtained in 76 % of the cases with both ointments Since even placebo gives good subjective results in musculoskeletal diseases like arthrosis, the necessity of double blind tests in studies of this type is emphasized because of the psychic components of these chronic diseases

DMSO has been used with good success in acute musculoskeletal diseases The experience obtained from chronic musculoskeletal diseases has not been equally favourable however and further information is needed in this field (1 2 4) DMSO used in conjunction with physical treatment has helped to shorten disease periods considerably This phenomenon has been ascribed to the following of the numerous qualities of DMSO DMSO 1) improves membrane penetration 2) is anti inflammatory 3) is analgetic 4) inhibits cholinesterase 5) acts as a vasodilator 6) relaxes muscles and 7) affects pathological collagen Normal collagen tissue remains intact (4)

Among the most recent studies is the double blind test by von der Hardt et al (3) who sought to ascertain whether DMSO solution locally applied has also a *central* effect According to them 84 % DMSO

solution applied to the area where pain was felt had an analgetic effect in 65 % of the cases and a similar effect was apparent in as many as 61 5 % of the cases when the same amount of DMSO was applied to a portion of skin at a distance from the painful area This seems to suggest that DMSO acts also centrally As the solution in question often caused erythema the results were controlled by using placebo rubnment in the same way There was a clear difference in favour of DMSO the figures being 60 % and 11 % respectively (3)

It has been noted earlier that DMSO solutions with concentrations ranging from 50 to 90 % do not essentially differ from each other in the manner of action and that the effect of solutions and ointments with concentrations below 10 % is comparable to the effect of placebo in acute musculoskeletal diseases (2 5 6)

The purpose of the present study has been to elucidate the effect of potent DMSO ointment and placebo ointment on pain sensations caused by arthrosis as the double blind method has not been used in correspond ing cases before

MATERIAL AND METHODS

100 outpatients with arthrosis of the knee joint who had felt almost *continuous pain in the joint for several years received ointment to be* applied on the joint three times daily for one month no preceding in formation about the quality of the ointment was given The ointment tubes were numbered and even the persons carrying out the experiment were unaware of the contents of each tube until the time when the results were classified After one month the patients were interviewed for their subjective impressions of the analgetic effect of the ointment The answers were divided into four groups the effect was 1) good 2) intermediate 3) poor when the patient was convinced that the ointment was ineffective and 4) indifferent when the patient had no definite opinion The average age of the patients was about 60 years The concentration of the *DMSO ointment was 50 % and the composition* of this as well as the placebo ointment has been presented elsewhere *

RESULTS

As it appears from the table surprisingly similar results were obtained from potent DMSO and placebo *76 % of the patients experienced the*

effect of the ointment as positive and only 8 % as poor while 16 % had no definite opinion No side effects were noted neither as local nor as general symptoms

DISCUSSION

As it is impossible to measure pain objectively the double blind methods are the only way to measure the effect of a given drug In topically applicable drugs components other than the effective one may cause a concrete sensation which in itself is experienced as unusual and is often expected to lead to positive results especially if the drug brings about distinct local changes such as erythema In prolonged illnesses also the psychic condition changes continually which must be taken into account when the results are considered In several studies positive results have been obtained in acute musculoskeletal diseases (1—5) It must be remembered however that damages of this kind often have a tendency for quick spontaneous recovery and that daily fluctuations occur which makes it possible for any drug to give even highly positive results Chronic diseases are more static in this respect and therefore also the analgetic results obtained from DMSO are more contradictory It is also true that many of the double blind studies conducted on DMSO

TABLE I

The Analgetic Action of 50 % DMSO Ointment and Placebo Ointment in Arthrotic Pain

No of patients		Positive good	Positive intermediate	Positive total	Poor	Indifferent
50 % DMSO	50	2 (44 %)	16(32 %)	38(76)	4(8 %)	8(16 %)
Placebo	50	25(50 %)	13(26 %)	38(76 %)	4(8 %)	8(16 %)

*) 50 % DMSO ointment

DMSO	1 500 0
Propylenglycol	250 0
Cetanol	250 0
Cremofor AP fest	500 0
Aq purif	250 0
Aetherol eucalypti	10 0

Placebo ointment

Propylenglycol	750 0
Glycerol	500 0
Cremofor AP fest	625 0
Cetanol	312 5
Aq purif	312 5
Aetherol eucalypti	10 0

do not fulfil the requirements imposed upon them Our results seem to suggest that a chronic patient is inclined to expect a positive result from any drug as soon as there is even a slight change for the better in his condition even when the change is only a cool layer of ointment or glowing erythema

In this connection can be mentioned the study in which DMSO solution applied far from the damaged point alleviated the pain felt in the actual damaged area practically as effectively as the solution applied directly to the hurting point would have done (3) this suggests that there exists a central route of action which is yet unexplained This German study does not report how many of the patients had an acute and how many a chronic musculoskeletal damage

The fact that only 4 % of the patients had a definite opinion about the ineffectiveness of the ointment is an indication of the above mentioned positively expectant attitude towards treatment and this is confirmed by the indifferent portion of 16 % in each group This makes it desirable to take an even more critical attitude towards topically applicable analgetic drugs also those not containing DMSO with the exception of local anesthetics proper

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8 Sept 1970

Vuopala U et al Acta Rheum Scand 17 61—6 1971

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DMSO IN THE TREATMENT OF DUPUYTREN S CONTRACTURE

A Therapeutic Experiment

By

U Vuopala and W J Kaipainen

Summary 25 patients who had had Dupuytren s contracture for over five years had 80 % DMSO lotion applied topically three times daily for one month Clinically significant improvement was not noted Four patients had a typical taste in the mouth Other side effects were not noted

It has been noted that DMSO dissolves pathological collagen but leaves normal collagen intact (3) Good clinical results have been obtained when keloids, scar tissues fibrositides, periarthritides scleroderma etc have been treated with DMSO (1—3) For this reason we decided to try a potent concentration of DMSO on Dupuytren s contractures of different degrees It has been noted earlier that DMSO solutions with concentrations ranging from 50 to 90 percent have approximately the same effect (2)

MATERIAL AND METHODS

23 outpatients who had Dupuytren s contractures of different degrees either in both hands or in one hand generally in the palmar aponeurosis of the V but also of the IV finger At the beginning of the treatment the distance between the top of the nail (cut) of the damaged

finger and the linea cephalica of the palm was measured when the finger was in maximal extension 80 % DMSO lotion was applied to the point of contracture three times daily for a period of one month After this the distance was re measured in a similar manner and if there was an increase of flexion it was interpreted as a positive result changes of less than 5 mm were not taken into account

RESULTS

In none of the patients did the flexion of the damaged finger change significantly They had all had the contracture for at least five years some had had it for over 10 years The results were somewhat better in the patients who had had the contracture for a shorter time but in all cases the increase of extension was less than 5 mm This 5 mm limit was chosen arbitrarily mainly with a view to estimating the practical significance Four patients had a taste in the mouth as a side effect

DISCUSSION

In treating acute musculoskeletal damages DMSO has been used successfully but enough information is not available concerning chronic damages In the present study it has been indicated that potent 80 % DMSO applied three times daily over one month is ineffective In most of these cases an operation was necessary There seemed how ever to be a slight suggestion that the effect was the better the more recent the change was It must also be noted that when the ointment was applied the patients themselves became actively *interested in the* state of the damaged finger and tried to bend and exercise it and that thus physiotherapy may consequently have affected the results It is necessary to use the 5 mm limit at least as a practical measure when evaluating the therapeutic effect

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IMMUNOGLOBULIN (IgA) DEFICIENCY IN SYSTEMIC LUPUS ERYTHEMATOSUS

Report of a Case and Family Studies

By

G L BACH V K G PILLAY and R M KARK

Summary A woman with an idiopathic convulsive disorder developed systemic lupus erythematosus (SLE) while on dilantin treatment The patient s serum was IgA deficient a finding which prompted study of all available members of her family Among 14 relatives low to absent IgA levels were found five times suggesting a genetically determined pattern of IgA deficiency Various clinical and laboratory data of the patient and her family are presented

INTRODUCTION

There have been numerous reports of immunoglobulin A deficiency occurring in patients with congenital and acquired agammaglobulinemia A selective absence of IgA on the other hand has been found in patients

This study was supported in part by grants from the U S Public Health Service from the Institute of Allergy and Infectious Diseases of the National Institutes of Health

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with ataxia telangiectasia (9 21 29) pernicious anemia (4 23) idiopathic epilepsy (18 28) sprue (6 7) chronic sinopulmonary infections (26 28) and in healthy adults (3 22)

More recently a selective IgA deficiency has also been reported in systemic lupus erythematosus (SLE) (2, 15) This is rather surprising since IgA levels in collagen diseases such as rheumatoid arthritis and SLE are commonly rather high (14 24)

In the light of these reports we would like to present a patient with SLE and the study of her family This patient developed SLE during the course of treatment with dilantin for longstanding idiopathic seizures and her serum IgA was found to be absent

PATIENTS AND METHODS

Case Report of Proposita H W

Mrs H W a 40 year-old white woman had a history of epilepsy since the age of 15 The seizures were controlled with 180 mg of phenobarbitone and 300 mg of dilantin daily During a two-year period the patient was admitted to the University of Illinois Hospital three times and closely observed otherwise in the outpatient clinic The patient s past history includes arthritis of 20 years duration for which she was treated intermittently with indomethacin and cortisone In 1950 she was told she had rheumatic fever She also gave a history of recurrent attacks of upper respiratory and urinary tract infections The diagnosis of SLE was made during her first hospitalization in June 1966 when she had sustained fever Coombs positive hemolytic anemia leukopenia high gamma globulins on zone electrophoresis and several positive LE preparations The response to steroids was prompt It is noteworthy that two months prior to admission mysoline had to be substituted for dilantin as the patient complained of a sensation of feverishness with the latter drug

She was readmitted in May 1967 with a history of dizziness instability of gait bizarre behavior and a butterfly rash on her face The blood urea nitrogen serum creatinine and beta 1c determinations were normal The urine sediment contained two erythrocytes and 4—5 leukocytes per high power field There was no protein in the urine The creatinine clearance was 75 ml per minute An intravenous pyelogram was normal Renal biopsy revealed a membranous glomerulonephritis with

local and focal hypercellularity The IgA was absent on immunoelectrophoresis Steroids were increased and the symptoms disappeared

The patient was admitted in June 1968 for investigation of absent serum IgA A second renal biopsy bone marrow aspiration and rectal biopsy were done Parotid saliva was collected with a plastic cup placed over Stensen s duct Skin tests with various antigens to check for delayed hypersensitivity were done using PPD histoplasmin blastomycine, brucella antigen and coccidioidin The patient was challenged by two injections of typhoid toxoid and influenza virus vaccine one month apart Chromosomal studies were also done

All available members of the patient s family were studied and the following tests were performed Serum IgG IgA IgM and beta 1c levels were measured by single radial diffusion using the immunoplates of the Hyland Laboratories Los Angeles California Rheumatoid factor titers were determined by a modification (1) of the standard method of Singer and Plotz (25) and by the rabbit gamma globulin latex fixation test (12) The presence of antinuclear antibodies was assessed using the commercial antinucleoprotein reagent of the Hyland Laboratories and an immunofluorescent technique (10) Immunofluorescence studies on the rectal mucosa and on the bone marrow were carried out employing fluorescein labeled monospecific antisera to IgG IgA and IgM Immunoelectrophoresis was done on all specimens and the precipitin arcs were developed with antihuman whole serum and monospecific antisera to IgG IgA and IgM

RESULTS

Figure 1 shows the immunoelectrophoretic analysis of the patient s serum (upper) and a normal serum (lower) control On slide no 5 the patient s serum shows rather heavy IgG and IgM precipitin arcs but no IgA line When monospecific anti IgA serum is used (slide no 6) the IgA is absent but can be clearly seen in the normal serum Slide no 7 shows again the heavy IgG precipitin line of the patient s serum as compared to a normal control serum

Skin tests for delayed hypersensitivity were negative in the patient for PPD histoplasmin and blastomycine A questionable erythema of less than 3 mm diameter with some itching followed the injection of coccidioidin and brucella antigen Titers to tetanus toxoid and to in

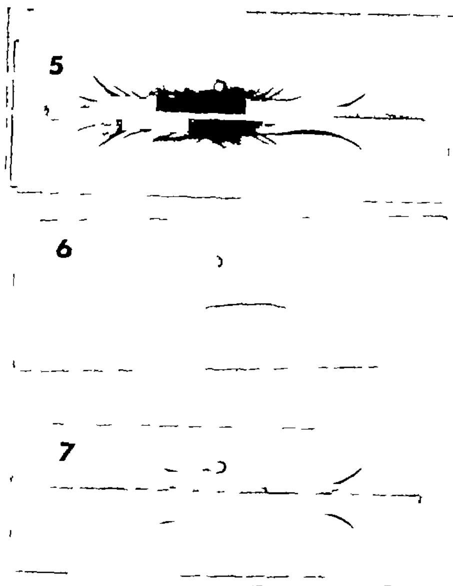


Fig 1 Immunoelectrophoretic analysis of patient (upper) and control serum (*lower*)

No 5 Against human anti whole serum Note absent IgA heavy IgG and IgM lines in patient serum

No 6 Against monospecific anti IgA. Note absent IgA in patient serum

No 7 Against monospecific anti IgG Note heavy broad bump IgG precipitate line in patient serum

fluenza A_2 Japan /170/62 remained unchanged as assayed before and after the booster injection Studies of the patient s concentrated parotid fluid (total protein = 10 mg/ml) did not show the presence of IgA However, the transport piece was present The rheumatoid factor remained constant at a titer of 1 160 Antinuclear factor tests were all positive Immunofluorescence studies of the rectal mucosa and the bone marrow did not reveal the presence of IgA forming plasma cells The renal biopsy showed membranous glomerulonephritis without proliferation Chromosomal studies were normal

Table I shows a summary of the major tests done on the patient and her relatives As can be seen IgA was also undetectable in the patient s father L H low in her brother G H at the lower limit of normal in her nephews L H and J W and in her niece L H These findings were corroborated by the patterns of the immunoelectrophoretic analysis It is noteworthy that her father and her brother have suffered since childhood from chronic respiratory infections Her father developed mumps at the age of 70 Although the patient s brother has a rather high IgA serum level he also has a long history of recurrent upper respiratory infections and so do propositus s nephew K H and niece L H The patient s mother has idiopathic epilepsy her sister underwent shock treatment for a psychological disorder and this sister s daughter A W nine years of age has increased IgG and IgM serum levels and a positive latex fixation test of 1 160 Thus only two members of the family showed a positive rheumatoid factor serology The latex rabbit gamma globulin test and the tests for the detection of antinuclear antibodies were negative in the entire family

DISCUSSION

IgA is recognized to be the predominant immunoglobulin protecting the mucous surfaces of the respiratory tract and the gut IgA forming plasma cells have been demonstrated in the bone marrow and rectal mucosa (5) Local production in submucosal cells and a specific transport system for IgA to the surface of the mucous membranes seem to be the mechanism involved (27) The occurrence of IgA deficiency in association with a variety of diseases is difficult to explain with regard to an etiologic significance Even more intriguing is the finding of IgA deficiency in normal individuals Thus Rockey et al (22) reported absence

TABLE I

Results in Relatives of Proposita H W

Relationship to proposita	Age (years)	Serum immunoglobulins (mg/100 ml serum) IgG	IgA	IgM	Beta 1c complement (mg/100 ml serum)	Clinical data
D (Family Tree)						
Proposita H W						SLE recurrent bronchitis and urinary tract infections idiopathic convulsive disorder
1st Admission	40	2340	0	186	108	
2nd Admission		2580	0	210	97	
3rd Admission		2420	0	196	102	
Son G W	20	1800	392	177 5	171	Failure to thrive pleurisy
Father L H	70	440	0	340	126	Asthma and bronchitis since childh
Mother M H	61	1400	240	153	08	Idiopathic epilepsy obesity
A (Family Tree)						
Brother G H	37 3/4	2030	16 4	82	188	Chronic chest condition
Daughter C	9 5/6	1575	147 5	96 5	199	Healthy
Daughter B	6 1/2	1290	162	196	175	Healthy
Son K	8	1375	195	107 5	150	Frequent upper res pir infections
B (Family Tree)						
Brother R H	31	1575	380	290	157 5	Allergies upper resp infections
Son L	5	825	62 5	114	154	Healthy
Daughter L	1 1/4	675	37 6	102	132	Frequent colds
C (Family Tree)						
Sister C W	44	1375	195	196	285	Shock treatments in the past
Daughter A	9	2160	221	142	171	Healthy
Daughter I	7	1375	224	114	166	Healthy
Son J	7/12	490	40	96 5	181	Healthy
Normal Range (for adults)		600 —1500	120 —380	60 —160	120 —200	

Lacking our own normals for the respective age groups these IgA levels were compared with the values given by Stiehm E R Fudenberg H H J Pediatrics 37 715 1966

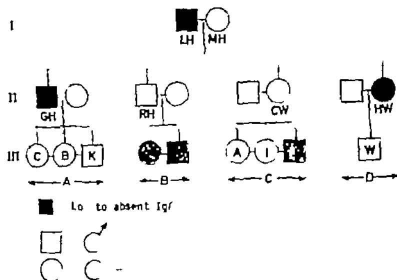


Fig 2 Family tree

of IgA in two healthy men without abnormal immunoglobulins of the other types in either proband's family Hanson (13) found 26 healthy persons lacking IgA Among 42 relatives of 12 IgA deficient individuals he found only one brother who had no IgA Goldberg et al (11) studied the family of a man with selective absence of IgA and found only one additional member of this family to have no detectable IgA McCroy and Kunkel (20) found among the relatives of a patient with SLE and absent IgA no other IgA deficiencies among the immediate relatives

The case we have presented is a rare one for several reasons IgA deficiency appears to be an uncommon finding it occurs only in 1 out of 500 or 700 individuals (3 15) The simultaneous presence of IgA deficiency and SLE has only been reported a few times (2 15 28) To our knowledge this is the first report of IgA deficiency in several members of a family Other intriguing data of this study are the finding of seizures in the patient and her mother in view of reports associating idiopathic epilepsy with SLE and lack of IgA (18 28) Furthermore the patient had been on dilantin treatment for many years Has this been

the trigger for the induction of SLE as has been suggested by some investigators (9 19 28)?

Chromosomal studies of the patient were normal and the ring 18 chromosome found by Finley et al (8) with IgA deficiency cases was not present The other members of her family were not available for chromosomal analyses

The patient presented in this study also deserves considerable interest in view of the obviously genetically determined pattern of IgA deficiency — as depicted in the family tree figure 2 — the character of which is as yet unidentifiable Goldberg et al (11) concluded from their study that the defect in certain individuals who selectively lack IgA is the inability probably genetically determined to synthetize IgA heavy chain Ignorant of the exact mechanism involved we would like to present two questions Has there been a genetic transmission of a condition which under the stress i e of chronic infection resulted in IgA deficiency among the susceptible members of the family studied by our group Or is the IgA deficiency congenital perhaps inherited as a recessive trait with incomplete penetrance

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STUDIES ON CYTO IMMUNOLOGICAL CHANGES OF THE SYNOVIAL FLUID IN RHEUMATOID ARTHRITIS

By

V Gligore H D Bolosiu Al Dutu and Aurelia Podut

Summary The comparative values of the rheumatoid factor titer the total hemolytic complement activity in the sera and synovial fluids of patients with rheumatoid arthritis, as well as the percentage of RA cells, have been determined in a selected series of 20 patients (16 sero positive and four sero-negative cases)

The most constant change — depression of the synovial fluid complement activity — correlated closely with the status of the joint involved with the degree of disease activity evaluated from the non specific inflammatory tests and the percentage of RA cells No such correlation was seen in this series as regards serum and synovial fluid rheumatoid factor titers

RA cells were found in a larger amount in the sero positive RA After lysis of the cells by freezing a latex agglutinating activity was seen only in the homogenates from the sero positive RA plots

In the last years considerable progress has been made concerning our knowledge of synovial fluid in different arthritides Thus a basis has been created for a better understanding of their pathogenesis In this paper we present our observations on interrelations between some parameters systematically investigated in a selected group of rheumatoid arthritis (RA) patients

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W are indebted to Behringwerke AG Hoechst Frankfurt for the delivery of necessary test material.

Table 1—Comparative values of the RF titer in sera (S) and synovial fluid (SF) in 16 patients with sero-positive RA

Reaction	S>SF	S=SF	S<SF
Waaler Rose	7	4	5
Latex-F-II	7	3	6

MATERIAL AND METHODS

Our study includes 20 patients with definite RA according to ARA criteria (5) 16 sero positive and four sero-negative The rheumatoid factor (RF) in the serum and synovial fluid was tested with Waaler Rose (Heller & Svartz modification) and Latex F II reactions For the assessment of the total hemolytic complement (C) in the serum and synovial fluid the 50 % hemolysis method was performed with the Kent Bucant Steiner technique modified by Punce (15)

The synovial fluid was examined cytologically (number of cells percentage of RA cells) the washed sediment was frozen at —20 C and then brought to room temperature several times with subsequent testing for the presence of RF with the Latex F II reaction (19)

RESULTS AND DISCUSSION

I Serum RF was present in a significantly increased titer in the 16 sero positive cases in at least one of the above mentioned reactions Hu

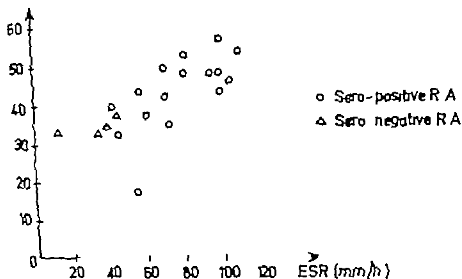
Table 2 - The mean values of the total hemolytic complement titer in sera and synovial fluids in 20 patients with definite R A (u H_{50})

Diagnosis	Number of cases	Complement Serum	Complement Synovial fluid	% of depres-sion
Sero-positive R A	16	50 60	6 40	86 56
Sero negative R A	4	39	4	87 50

man anti gammaglobulin RF was found more frequently (12 cases titers between 1/20—1/640) than rabbit anti gammaglobulin RF (9 cases titers between 1/32—1/1024) The highest values were found in the long time severe cases with polyarticular and visceral involvement, and subcutaneous nodules In this respect our findings are consistent with current data in the literature (6 7 8 9 17 21)

II RF in the synovial fluid was present in titers varying between 1/32 and 1/512 with the Waaler Rose reaction and between 1/40 and 1/320 with the Latex F II reaction in all cases of sero-positive RA Comparative values to serum titers are described in table I We shall not discuss these differences because of the small number of cases and the paucity of relevant data concerning synovial permeability both in normal and pathological states (14) In the sero-negative cases RF was also absent in the synovial fluid

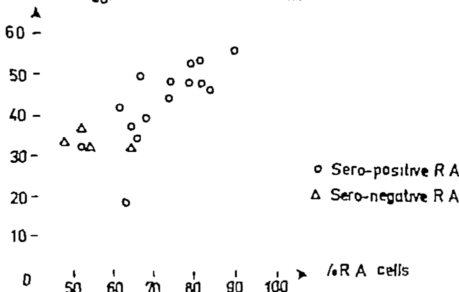
III The serum C in our series varied from 55 to 62 C H_{50} units with a mean value of 50 6 ± 5 3 CH_{50} u in sero-positive and 39 ± 5 02 CH_{50} u. in sero-negative RA In a single previously reported case with malignant RA the serum C was lower than 10 C H_{50} u (3) Normal serum C levels have been established by titration of 12 normal sera The values ranged from 55 to 62 CH_{50} u with a mean



of 44 35 ± 4 65 C H_{50} u which is not far from Peltier's 42 5 C H_{50} u (14)

IV The synovial fluid C varied from 0 to 19 C H_{50} u As normal synovial fluid C levels we consider 21 ± 2 5 C H_{50} u which was found previously in five patients with post traumatic hidarthrosis of the knee joints The mean values of the differences between serum and synovial fluid C was 43 8 C H_{50} u for the seropositive and 34 25 C H_{50} u in the sero negative RA which means a percentage of depression almost equal between the two groups 86 56 % versus 87 5 % (Table II) Correlating this characteristic depression of synovial fluid C (10 11 12 24 25 26) and other parameters investigated (correlation coefficient r Guilford) the following data were noted

a Synovial fluid C depression does not seem to have any significant connection to the presence or titer of RF ($p = 0.05$) nor to the number of cells in the synovial fluid ($p > 0.10$)



b A correlation was found between the state of the respective joint the non specific inflammatory tests especially ESR ($p < 0.01$) and the percentage of RA cells ($p < 0.01$) (Graphs 1—2)

Our results are consistent with those of Peltier et al (14) but are at *variance with some of Hedberg* (12) *In order to explain the relative* independence of the depressed synovial fluid C from RF the following hypotheses should be discussed a) fixation of C by aggregated IgG (10 22) b) different behaviour of RF towards synovial fluid C function antigen antibody ratio in the immune system (18 20) and c) contribution of other immune aggregates in the fixation of C (22 23)

V RA cells were present in all cases studied Their percentage (to 100 pmn leukocytes) varied from 48 to 88 with a higher mean value for sero positive RA (72 %) than for sero-negative RA (54 5 %) Four cases from the sero-positive RA group have been compared with the four sero negative cases as regards the property of leukocytes from the synovial fluid sediment to release RF after cell rupture through phys

cal methods The Latex F II test was positive following the above mentioned procedure at the borderline titer of 1/20 only in the sero positive RA our data being at variance with some papers (1) Previously we had similar negative results in three cases of rheumatic fever with an average value of RA cells of 23 % (4) We consider these data as an argument in favour of the RF content of the inclusion bodies in RA cells from sero-positive RA Thus a connection exists between the prin cipal immunologic change and the sequence of events in the rheumatoid joints phagocytosis of immune complexes lysosomal alterations release of phlogogene enzymes synovial and cartilaginous damages (1 2 13 19 22)

CONCLUSIONS

The most constant immunologic finding in synovial fluid of RA seems to be the depression of C contrasting with normal or slightly increased serum values This finding is consistent with an auto-immune event occurring in the rheumatoid joint where IgM RF aggregated IgG is not the only incriminated system We consider the depressed synovial fluid C to have a great diagnostic significance and hold that it can be developed as a reliable test in assessing the results of immuno-suppres sive therapy both local and general

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HISTOCHEMICALLY DEMONSTRABLE CHANGES IN LACTATE AND SUCCINATE DEHYDROGENASES IN NORMAL RABBIT SYNOVIAL MEMBRANE AFTER INJECTION OF OSMIUM

By

M MOTTONEN K KARLOLA M PANTIO & T NEVALAINEN

Summary The changes in lactate dehydrogenase and succinate dehydrogenase activities caused by osmium tetroxide were examined histochemically in normal synovial membrane of the rabbit. The animals were albino rabbits and they were 18 altogether 0.3 ml of 1 % OsO_4 solution was injected i a in the right knee The left knee joint served as a control One day after the injection decrease in the enzyme activities was observed around the osmium particles deep in the synovial tissue as a sign of necrosis Enzyme activity stronger than normally was seen after one week in the newly formed granulous tissue It appeared both in fibroblasts and foreign body giant cells Because lactate and succinate dehydrogenases indicate the changing energy production in traumatized tissue, these enzymes thus demonstrate the onset of the regeneration process one week after the injection of OsO_4

Osmium tetroxide has been used in local treatment of painful affections of rheumatoid arthritis especially when conservative methods

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This work was supported by grants from Sigrid Juselius Foundation Helsinki, and the National Research Council for Medical Sciences in Finland

with the hydrops have been unsatisfactory The depth of tissue penetration of this agent is probably rather small (2) The effect of the injection has been described by the name chemical synovectomy

Osmium tetroxide is a strong oxidizer In contact with organic substance it is very rapidly reduced to lower oxides and thereafter is entirely inert (8) Osmium causes arrest of the blood flow in the synovial intimal layer (2) and has a specific affinity for the tissues affected by the rheumatoid process (4) Osmium penetrates relatively rapidly under the endothelium which is necrotized by it Thereafter an infectious process begins and it is followed by formation of granulous tissue Numerous foreign body giant cells and fibroblasts are seen around the osmium particles It is possible that the primary effect is rather superficial and a strong scar tissue is formed secondarily (6)

The accurate mechanism and depth of the effect cannot be interpreted with certainty by ordinary histological methods It is difficult too to determine the time of the beginning of the regeneration process That is why lactate and succinate dehydrogenases describing primarily energy metabolism have been used in the present investigation in order to elucidate the effect of osmium injections

MATERIAL AND METHODS

The experiments were carried out with 18 albino rabbits of both sexes about one year old and about three kg by weight An intraarticular injection of 0 3 ml of 1 % solution of osmium tetroxide in physiological saline was given into the right knee when the animals were slightly anesthetized with Nembutal The left knee served as a control The rabbits were killed with an overdose of Nembutal and the tissue specimens were taken two hours (3 animals) 24 hours (3 animals) 48 hours (3 animals) 1 week (3 animals) 4 weeks (3 animals) and 7 weeks (3 animals) after the osmium injection The specimens were immediately frozen in isopentane which was frozen down to —70 C in a mixture of acetone and dry ice Sections were cut in a rotary microtom at —20 C The section thickness was 16 mμ The activity of lactate and succinate dehydrogenases was demonstrated histochemically The incubation procedure was carried out according to the method of Balogh *et al* (1) The tetrazolium salt used was Nitro BT



Fig 1 Lactate d hydrogenase activity of the synovial tissue 2 days after the osmium tetroxide injection To the left, black osmium s irregular granules and to the right, normal connective tissue are observed In the center especially in the lower part, an inactive zone is seen (101 x)

RESULTS

Lactate Dehydrogenase

Fibroblasts which were rather scattered in the endothelium and adipose tissue of the normal joint synovial membrane were excluding the nuclei active and thus clearly stained The fat cell membranes were sporadically clear The medial layer of the arteries and striated muscle sometimes visible were also distinctly active

No changes in the activity could be seen after two hours of the osmium tetroxide injection The osmium tetroxide which had penetrated under the endothelium could be seen as black particles

After one and two days an unstained inactive zone was noted around the osmium particles This zone was of varying breadths and bordered accurately on the surrounding adipose tissue Even the arteries had lost their enzyme activity in this area In some places osmium had spread



Fig 2 Lactate dehydrogenase activity 4 weeks after the osmium tetroxide injection To the left and in the lower part, osmium granules and giant cells around them are seen Around the osmium and in the center strongly active proliferative connective tissue is observed (52 x)

on the surface of the adipose cells as veil like formations These veils were stained by atypical crystalline indicator (formazan) Enzyme activity appears as small granules in the cells

One week after the injection inactive tissue was seen only scattered and in a very narrow zone around the osmium particles The activity and number of fibroblasts had clearly increased Thus the activity of the whole tissue had increased

After four weeks the osmium particles were observed in a very active granulous tissue containing fibroblasts There were strongly stained particularly active foreign body giant cells around every osmium particle Hardly any adipose tissue was observed

After seven weeks no adipose tissue could be seen but the whole synovial tissue was formed of fibroblasts and connective tissue Active foreign body giant cells were still observed round the osmium particles

Succinate Dehydrogenase

In normal synovial membrane succinate dehydrogenase showed weaker activity than lactate dehydrogenase The location of succinate dehydrogenase was similar to that of lactate dehydrogenase

Two hours after the injection the osmium particles were the only exception from the normal picture

After one and two days an unstained inactive zone was observed around the osmium granules as with lactate dehydrogenase The zone was however broader than with lactate dehydrogenase especially after two days The veil like layer of osmium on the surface of fat cells was stained by a crystalline stain

After one week the activity had receded Strongly stained fibroblasts were numerous The inactive zone had disappeared Activity was strongest around the arteries

After four and seven weeks active fibroblasts were noted around the osmium particles but their activity decreased when the distance became greater Giant cells were only faintly stained

There were no marked differences in the histochemical reactions to the osmium tetroxide treatment between the animals within a given experimental group

DISCUSSION

In normal synovial tissue both lactate and succinate dehydrogenase activities were noted in synovial cells and the walls of the arteries Previously Campbell (3) observed ATPase activity in the same elements of the rabbit synovium

From one hour onwards rather superficial necrotizing of the synovial tissue was observed histologically (6) Enzyme histochemically decrease and disappearing of enzyme activity indicating injury of the tissue was noted considerably deeper in the tissue Decrease of succinate dehydrogenase indicates inactivity of the Krebs cycle and decrease of lactate dehydrogenase also discontinuation of anaerobic oxidation These facts must be a sign of a severe tissue injury which extends in a wide area around the osmium particles and can be seen clearly one day after the injection The changes resemble enzyme histochemical changes caused by anoxia or ischemia (7) Lactate dehydrogenase describing anaerobic metabolism is less severely affected

Within one week the regeneration process begins, and it is seen as enzyme activity stronger than normally in the fibroblasts Foreign body giant cells show strong lactate dehydrogenase activity indicating that anaerobic glycolysis has temporarily replaced more complete aerobic oxidation Mori et al (5) have noted strong activity of this enzyme in giant cells

The character of the crystalline staining which is atypical for an enzymatic reaction caused by the veil like osmium layer is still unclear but it may be a non specific reduction of tetrazolium catalyzed by osmium in necrotizing adipose tissue

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18 Sept., 1970

Notice
from the Editor

At our meeting in Copenhagen last year it was decided that at the side of the Editor and the Editorial Secretary Acta Rheumatologica Scandinavica should have one representative as subeditor for each national association of rheumatologists grouped under Redactores Each subeditor will be assisted by a group of referees representing different special fields of research

The change has been put into effect from issue no 1 1971 and is undertaken in order to simplify for contributors to have their papers examined more rapidly

for Nordisk Reumatologisk Forening

The Editor

Brattst em H & M Acta Rheum Scand 17 86—93 1971

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LONG TERM RESULTS IN KNEE ARTHRODESIS IN RHEUMATOID ARTHRITIS

By

HAKAN and MERETE BRATTSTROM

The importance of close cooperation between the rheumatologist and the othopedic surgeon is again illustrated in the present paper

The Editor

Summary A follow up study is done on 45 knees in 43 patients with rheumatoid arthritis, fused ad modum Charnley Mean observation time seven years (4—14 years) Biomechanical problems concerning compensation of leg length difference are discussed 39 patients with 41 fused knees were satisfied Reasons for dissatisfaction in four cases are given Three patients continued to use the unfused knee as standing leg The movable knee deteriorated in 25 knees in all of which a valgus and/or flexion deformity was established Twenty three patients had plantar flexion contracture and/or fore foot destructions on the fused side The importance of adequate post operative management (quadriceps training compensation for leg length difference by raising both sole and heel and ergonometric instructions) is emphasized

Is it justified to fuse a knee in patients with rheumatoid arthritis with general joint involvement? With increasing possibilities of performing knee arthroplasties the question may be of interest to evaluate

Read at the 13th Scandinavian Congress of Rheumatology in Copenhagen June 1970

By giving the patient one stable standing leg it is on one hand stated that the other knee often also involved can be spared On the other hand a knee fusion in an arthritic patient with bilateral knee involvement may subject the other knee to a greater strain and accelerate the course of the disease there It is known that the patient is primarily satisfied with his painless stable knee but about the long term results, when the patient's memory of the painful pre operative condition has faded and other joints have gradually become involved we know little

The aims of this follow up investigation were to ascertain

1 The patient's opinion about the operation and reasons for dissatisfaction
2 Did the patient use the fused leg as a stable standing leg?
3 Has the course of the disease in other joints of the lower extremities been influenced by the arthrodesis and in which direction?
4 Has the pre and post operative treatment been adequate or can it be improved
5 Shall we continue to fuse severely destroyed knees?

Patient Material

From 1956 to 1966 knee arthrodesis was performed in 63 knees in 61 patients with definite or classical RA (ARA criteria) 45 knees in 43 patients are included in the follow up study (Excluded 4 more than 85 years of age 9 dead and 5 not found) Mean age at operation 52 years mean duration of disease 16 years Mean observation time 7 years minimum 4 years Indications for arthrodesis were severe destructions with pain instability and/or decrease of function because of severe contracture Involvement of the other knee was present at the time of operation in all cases and this was regarded as a factor in favour of the operation The fusion of the most involved knee was performed to postpone the destruction of the best one During this period practically no other operations were performed in severely destroyed arthritic knees

All patients were operated according to Charnley's method with compression instrument A position of 5—10 of flexion was aimed at The compression instrument was removed after 4—6 weeks and the patient was provided with a plaster cylinder for another 6—8 weeks and permitted to start weight bearing

All except one fused (Case 1) One patient developed an infected fistula (Case 3) otherwise no noteworthy complications occurred

At the follow up the patients were evaluated

1 Clinically
2 Roentgenologically including weight bearing in valgus and varus provocation
3 26 patients were examined through a 20 minute test on a balance scale registering the percentage loading of right and left leg respectively

Patient's Opinion

39 patients with 41 fused knees were highly satisfied or satisfied with the result of the operation Two patients were dissatisfied and two patients were moderately satisfied

These last four patients deserve a short analysis

Case 1 Woman, 74 years old at operation, long term steroid treatment The knee did not fuse general condition became worse she became wheel chair bound regrets the operation

Comment wrong to do the operation at 74 years especially if the patient is on steroid treatment

Case 2 Man, 51 years old at operation Admits the advantage of a painless stiff knee but feels cheated because he did not realize before, that the leg was going to be stiff

Comment a complete information to the patient pre operatively is selfevident

Case 3 Woman 53 years old at operation, developed infection round the compression pins and has had several years of periodical infections

Case 4 Woman 72 years old at operation, developed painful corns under the metatarso-phalangeal joints of the fused side and this she attributes to the operation

Comment too old for knee fusion was not compensated for the leg length discrepancy (see below)

Fused leg as standing leg? The patients were asked which leg they used as the standing leg and 26 patients were tested on the above mentioned balance scale There was a consistent agreement between this investigation and the patient s own opinion about loading Eleven loaded the fused knee more than 70 % 4 between 60 and 70 % 8 patients equal Three patients had not discovered the advantage of the stable standing leg and continued to put most of their weight on the movable leg

Effect on other joints Are the deteriorations seen in other joints in the legs only part of the natural course of the disease or is there a biomechanical influence of the fusion? Discussing these problems one must not forget that if a partly wheel-chair bound patient starts walking because she is relieved from a severely painful knee all loaded joints will be strained this regardless of how she uses her legs

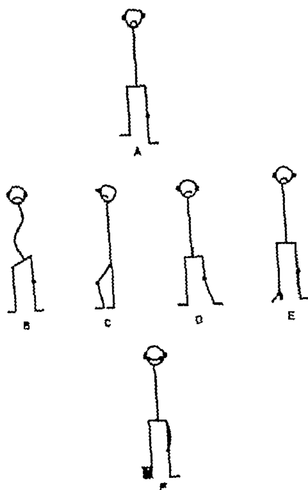


Fig 1 Different ways to compensate for leg length difference, see text.

There is a possible biomechanical explanation responsible for the changes seen in the other joints By shortening the fused leg 3—4 cm a leg length discrepancy arises (Fig 1 A) which can be compensated for in the following ways

Fig 1 B By tilting the pelvis towards the operated side and developing thereby a functional scoliosis (unusual in rheumatoids)

Fig 1 C + D By flexing the longer leg and holding it in slight valgus position or

Fig 1 E Plantarflexing the ankle joint of the operated side to eliminate the discrepancy

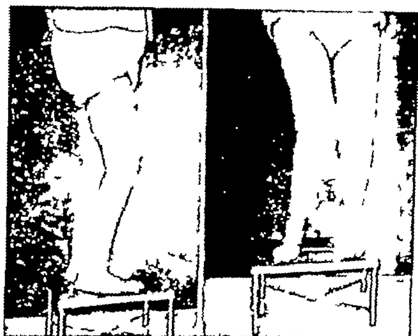


Fig. 2 A and B. Left knee fused. The patient has compensated for the length difference by placing the movable right knee in position of slight flexion and valgus. Result: Flexion contracture and increasing deterioration of the lateral joint space.



Fig. 2 C. X-ray from the same patient. Note the depression of the lateral tibial plateau.

TABLE I

Details about 25 Deteriorated Knees

Comparison between the objective findings in the non fused knees at the follow up and the time of fusion of the other knee

21 had developed flexion contracture ≥ 15

25 had developed lowering of *lateral* joint cartilage on the x ray film of these 21 had lowering of both lateral and medial cartilage but the *lateral* deterioration dominated in all cases (as a result of valgus position)

17 had developed compression of the *lateral* tibial condyle of these 7 had compression of both lateral and medial condyle but the *lateral* compression dominated in 5 cases in it was equal (valgus position)

No patient had either lowering of the medial joint cartilage or compression of the medial tibial condyle as a single entity

For a patient with for instance an osteoarthritic fused knee these different ways will mean little but for a patient with rheumatoid arthritis with a general joint involvement the risk of fixed contractures is serious The patient may develop a flexion contracture in the flexible knee which is also loaded in a valgus position or may develop a fixed plantar flexion in the ankle joint with consequent overloading of the metatarso-phalangeal joints and painful corns under the forefoot

Hips The disease had progressed (evaluated clinically and by x ray) *bilaterally* in eight patients In six patients only the contralateral and in three the hip on the fused side had become worse This does not seem to support the theory of abnormal strain on the hip of the fused side

The flexible knee 25 knees of 41 deteriorated considerably The knees had clinically an almost identical picture of fixed flexion contracture and valgus position in the movable knee and instability sideways (Fig 2) The x ray changes are shown in table I and fig 2 C

No certain difference could be found between the 25 deteriorated and the 18 unchanged movable knees concerning time of observation age at operation duration of disease and activity of disease

Out of the 25 deteriorated knees 18 were operated on 2 arthrodesis 7 MacIntosh arthroplasties 5 osteotomies and 4 late synovectomies The remaining 7 were for different reasons (lack of co-operation age permanently wheel chair bound) not suitable for further operations

Foot and ankle joints 21 of 43 patients developed lack of dorsiflexion and/or fixed plantar flexion in *the ipsilateral* ankle joint together with

varying degrees of fore foot changes painful corns etc on the same side Four patients had fore foot troubles on both sides but none had these problems only in the non fused leg This is what will be expected from the biomechanical way of compensating for the leg length difference (Fig 1 E)

In most cases the fore foot troubles have been eliminated by raising the heel and the sole of the fused leg and/or by performing a resection of the metatarsophalangeal joints

Can the Pre and Post Operative Treatment be Improved?

From our present experience and the above mentioned figures of complications from other loaded joints we assert that an adequate pre and post-operative treatment should include the following

1 Training of quadriceps muscle of the movable knee In order to minimize the risks to the joint the training should be static Fig 1 F

2 Post operative compensation of leg length discrepancy by raising the sole as well as heel of shoes to avoid overloading of the fore foot Fig 1 F

3 Education of the patient to use the stable knee as much as possible and to save the flexible one in daily life for instance by walking backwards downstairs using the right technique in transferring using catapult chairs and portable seats etc

4 Last but not least the patient should be under control by a rheumatologist and/or an orthopedic surgeon every six months to meet the problems in other joints which will undoubtedly appear

None of the 43 patients received the above mentioned post-operative treatment 14 had made use of a leg length compensation on the heel only in 3 of these 14 patients it was later removed by a doctor who felt that the patient would be better off without it Frequency of complications in the ipsilateral foot was the same in the compensated and non compensated patients

Shall We Continue to Fuse Severely Destroyed Painful Knees?

We know now that other operations (arthroplasties high osteotomies and late synovectomies with debridement) in experienced hands and with adequate post operative treatment can give good results but also that the complications (especially with arthroplasties) can be severe We feel convinced that an operation with which 39 patients out of 43 feel satisfied after an average of seven years observation time is a safe

alternative especially in hospitals where surgical rehabilitation of patients with RA is not a daily routine but the post-operative training and regime is of great importance

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METABOLISM OF FIBRINOGEN IN PATIENTS WITH RHEUMATOID ARTHRITIS AND IN A CONTROL GROUP

By

R Bach Andersen and Th Friis

Summary I^{131} fibrinogen turnover rate was examined in 27 patients, 15 patients with RA and 12 patients with various diseases Fractional catabolic rate was identical in the two groups and a difference was found only in the mass of fibrinogen g/day mean turnover being twice as high in the RA In countings of radioactivity of the inflamed joints a correlation to activity of the disease was found Intraarticular injection of I^{131} tagged fibrinogen into two patients with RA and into two patients with no joint complaints showed some deviation in proportion of clot /plasma activity In RA patients a tendency to resorption of fibrinogen from the joint was observed and in the controls a tendency to local lysis

Exacerbation in rheumatoid arthritis (RA) is followed by an increase of fibrinogen and an increased inhibition in the fibrinolytic activity of plasma (2 6) and synovial fluid (5) Furthermore an increase of fibrin deposits in the inflamed area has been found These changes may influence the metabolism of fibrinogen

There is a general agreement that the fibrinogen catabolism is a first order process The half life in normal human subjects studied with S^{35} methionine incorporation in vivo I131 tagged fibrinogen in vitro and fib-

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rinogen transfusion into patients with congenital afibrinogenemia differ from 2.1 to 4.3 days (5, 7, 11, 14, 20). Adelson in his monograph (1) finds that the most reliable studies are recorded by McFarlane and his group (14, 15, 16). In their studies the half life for plasma fibrinogen in normal subjects ranges from 2.1 to 3.8 days with an average of 3.1 days which corresponds to a catabolic rate in normal humans of 31± 6 % of plasma fibrinogen per day, and as the plasma fibrinogen represents 73± 15 % of the total body fibrinogen, the turnover found corresponds to a turnover rate of 23.2 % of the total body fibrinogen per day.

In abnormal states no significant changes in fibrinogen catabolic rate have been reported. However, some authors dealing with patients with arteriosclerosis (17) and patients with RA (19) have found increased catabolic rate.

In the experiments to be described an attempt has been made to study the plasma fibrinogen turnover (with I^{131} tagged fibrinogen) together with the local turnover (affected joints) in a group of patients with RA with various degrees of the disease compared to a group of inpatients without inflammatory joint diseases.

MATERIALS AND METHODS

Clinical material. The patients (Table I) were selected at random among inpatients. The RA group comprises 17 patients, 14 with classical and 3 with definite RA according to the criteria of the American Rheumatism Association with a duration of 1/2 year—28 years (mean 5 years). The control group comprises 14 patients with various diseases. The activity of the disease in the RA patients was judged by Lansbury's Clinical Index (12).

Human fibrinogen with I^{131} was obtained from Philips Duphar, Holland, with an activity of 0.065—0.414 mc/mg fibrinogen corresponding to 0.—0.5 atoms per molecule of the protein. In agar gel electrophoresis a single protein band was found in the beta globulin area, which corresponded to the known migration of fibrinogen, KABI A/B Stockholm, Sweden. The fibrinogen I^{131} was dissolved just before use in 0.15 M NaCl and an amount of 50—150 μC was given i. v. at 8 a. m. the first day (mean clottability = 94 ± 5 %). *Bovine Thrombin*, Park Davies, stock solution 1.000 unit/ml. (Final concentration 10 unit/ml. plasma).

TABLE I

Catabolism of I¹³¹ Fibrinogen in RA Patients and Patients without Inflammatory Disease

Case number	Condition		Wt kg	Sex	Age years	Plasma volume l	Lansbury clinical index	ESR mm/hour	Plasma fibrinogen pool	Catabolic % day	Rate g/day
1	RA	Classical	75	M	60	3 8	45	24	17 5	6 1	4 55
	—	—	71	M	58	4 0	45	18	19 1	29 4	5 62
3	—	—	57	F	54	3 4	68	17	15 1	28 9*	4 56
4	—	—	65	F	70	3 8	35	20	16 5	25 6	1 5
5	—	—	71	M	65	3 6	70	58	22 3	28 9	6 45
6	—	—	62	F	64	2 4	50	50	11 7	24 7	2 87
7	—	—	50	F	63	2 4	30	25	9 5	28 8	2 74
8	—	—	42	F	58	2 0	50	52	11 6	25 2	2 94
9	—	—	40	F	64	2 4	134	90	20 6	30 1	6 39
10	—	—	59	F	65	3 1	40	45	15 1	22 0	5 36
11	—	—	52	F	65	3 0	81	65	15 8	27 8	4 37
12	—	—	63	M	78	5 5	100	84	17 4	29 7*	5 19
13	—	definite	57	F	68	2 9	—	49	14 2	19 0	2 70
14	—	—	70	F	64	2 4	—	21	11 4	51 5	3 58
15	—	—	57	F	54	2 2	—	60	1 5	28 2	3 45
Mean			57		63	§3 0±0 7			**15 8±3 6	*27 1±3 3	** 4 19±1 26
16	Pyelonephritis		82	F	59	2 1	—	121	9 4	52 9*	5 10
17	Osteoarthrosis		58	F	70	2 3	—	15	7 5	26 1	1 98
18	Osteoarthrosis		62	F	66	2 4	—	6	7 4	23 1	1 71
19	Spondylosis		—	F	67	1 7	—	11	6 9	34 6	2 41
0	Spondylosis		45	F	48	2 5	—	11	9 1	30 7	2 81
21	Gastritis		49	F	40	2 7	—	25	9 8	24 8**	2 20
22	Hepatitis		75	M	89	3 1	—	21	10 7	20 4	2 20
23	Neurosis		64	F	56	2 2	—	16	12 3	25 6	3 16
24	Colitis		58	F	68	2	—	6	7 4	21 5	1 57
5	Nephrolithiasis		60	F	62	1 4	—	—	6 5	27 7*	1 74
6	Neurosis		64	M	48	2 5	—	2	7 9	30 6*	2 43
27	Adipositas		76	F	60	2 5	—	9	10 8	27 7*	2 90
Mean			63		60	§2 5±0 4			**8 8±1 9	***27 3±4 5	***2 35±0 55

Tl ur ne collection these cases was evidently not sufficient
= 6 07 p<0 001
= 0 9 p>0 1

*t = 4 73 p<0 001
** 3 33 0 0 >p>0 001

All patients were given a solution of potassium iodide (10 300) 15 g three times a day for 2 days preceding the study and during the study to prevent the thyroid uptake of I^{131}

Counting plasma samples (1 part Na citrate 3 5 % and 9 parts blood aminocaproic acid in a final concentration of 10^{-2}M centrifuged at 3 000 rpm) were collected after 20 min 4 6 24 30 hours and on the 3rd 4th 5th 6th and 7th day at 8 a m In plasma the total activity the protein bound activity after precipitation with trichloracetic acid, 10 % super natant activity and fibrinogen activity clot clotted with thrombin, was determined The clot was washed twice and redissolved in 40 % urea of the same volume as the ordinary plasma sample before determination The serum was also tested At least a count of 2 000 (error = 2 %) was counted

At the same time standard I (1/10 of the given initial dose for urine specimens) and standard II (1/100 of the given initial dose for plasma specimens) were prepared Standard I and twenty four hours urine were assayed in a scintillation detector in a volume of 1 1 standard II and plasma samples were assayed in a well scintillation crystal detector in a volume of 5 ml Thus the twenty four hours urine and the plasma samples were expressed in percentage of the respective standards (initial dose) Blood volume was determined in Volemetron using 5 μC I^{131} albumin after equilibrium time of 10 min Fibrinogen was determined according to Bang (4) (normal range 200—400 mg %)

Figure 1 shows a typical set of results The fact that the injection of the I^{131} tagged fibrinogen as used here was followed by a relatively rapid initial fall in plasma radioactivity and after approximately 1 or 2 days a more gradual decline appeared which may point to a rapid initial degradation due to denaturation of the fibrinogen But as illustrated in the example of table II the figures of which contain the countings for one patient no larger initial increase in non protein bound radioactivity was found

The mean half life time of 63 hours for all the patients counted on the plasma fibrinogen clot (mean clottability 94± 5 %) corresponds to a fractional elimination rate of 26 4 % of the total body pool per day (fractional elimination rate $k = \frac{\ln}{T\frac{1}{2}}$) This means that if the intravascular pool represents 80 % as shown by McFarlane this corresponds to a catabolic rate of about 33 % of the fibrinogen in plasma In this

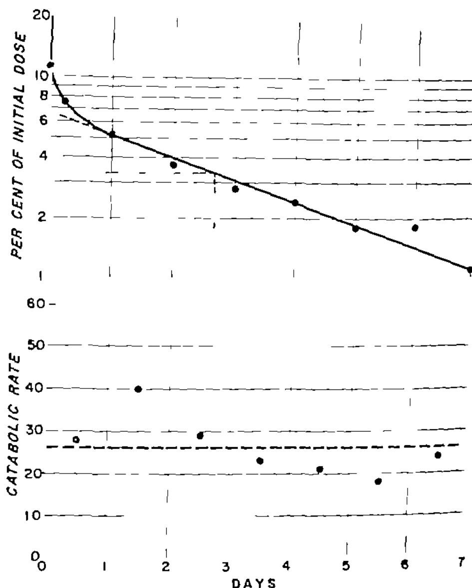


Fig 1 I[131] fibrinogen survival in case 1 Catabolic rates (lower diagram) are 24 hours urine radioactivities expressed as a percentage of the mean protein bound radioactivity in the plasma on the same day

experiment the extrapolation intercepts of the plasma exponential were lower than reported by McFarlane (14) (mean 63 % range 54—80 %)

TABLE II

The Correlation of Radioactivity in Plasma Serum and Clot in Case 4

The percents indicate percent radioactivity of the administered dose per l serum

Day	Plasma %	Serum %	Precipitated Plasma Protein %	Precipitated Serum Protein %	Clot
1	16 6	0 8	16 4	0 50	14 1
2	8 4	0 6	6 5	0 22	7 7
3	5 6	0 2	5 1	0 11	5 4
4	4 0	0 13	5 4	0 07	5 9
5	3 0	0 13	2 8	0 17	5 5
6	2 6	0 09	2 5	0 07	3 2
7	1 9	0 05	1 9	0 07	1 9

By calculating the catabolic range by the more direct procedure of dividing 24 hours urinary activities by mean plasma activities on the same day a mean of 27 7 % range 20 %—37 % was found Obviously the urine collections were not sufficiently collected in 9 cases (6 control patients and 3 patients with RA) Thus the first mentioned calculation has been chosen well knowing that the values found of plasma fibrinogen (g/day) are too low which however does not influence the proportion searched between RA patients and the controls

RESULTS

Turnover Rate

Fibrinogen was determined daily and showed no fluctuation in the two groups during the study which may indicate that the patients were in a stable state (mean for the RA 526 mg/100 ml mean for control 359 mg⁻) The RA patients judged as a group generally showed a higher value of plasma volume (mean 3 0 l range 2 0—4 0 l for the control mean 2 4 l range 2 1—3 1 l) In contrast no significant differences were found between the two groups in respect to the determination of the half life or the fractional catabolic rate However a difference of the mass of fibrinogen turnover (g/day) of about twice was observed depending only on activity of disease No significant difference was observed in urine excretion between the two groups especially no delay in the RA group was found

TABLE III

Counting of Joints in % of Soft Tissue

Case number	Soft tissue %	Knee left	Knee right	Wrist left	Wrist right
			RA		
8	100	79	77	53	54
9	100	195	176	93	116
10	100	102	192	83	89
11	100	88	94	73	81
12	100	155	155	104	99
13	100	110	115	77	91
14	100	183	96	56	67
15	100	104	114	167	153
			Controls		
22	100	69	66	51	51
23	100	71	75	77	54
24	100	72	73	52	49
25	100	94	76	42	58
26	100	74	84	50	58
27	100	79	83	64	65
Mean		75%	75%	56%	55%

Osteoarthrosis

Counting of the Joints

In eight RA patients and in six control patients (four patients with dyspepsia and two with osteoarthrosis) countings of knees and wrists were compared to countings of the soft tissue 15 cm *proximal* to the knees (cylindrical collimator 5 cm in diameter and scintillation crystal detector were placed at distances from the measuring areas of 1 and 16 cm respectively) The countings of the soft tissue on the two sides in the two groups showed no significant differences In the calculation *the soft tissue radioactivity was set to 100 % and in the control group* the countings of the knee showed a mean of 75 % (range 71—94 %) of the wrist a mean of 55 % (range 42—77 %) The RA patients varied in accordance with the clinical state of the joint (temp of the skin the thickness of the capsule and effusion of the joint) Cases of low activity countings as in the control group were recorded and in the rest depending on activity the values observed were higher (see table *III*)

TABLE IV

Proportion of Clot/Plasma (%) after Intraarticular I^{131} Fibrinogen

Day	Normal knee A	B	RA knee C	D
1	40.5	17.3	48.2	50.0
	52.8	26.5	6 7	96.5
	34.5	58.5	68.9	96.2
	52.2	—	78.6	61.0
3	46.2	68.5	81.0	45.3
4	41.5	61.6	—	67.3
5	40.7	61.2	91.0	71.0
6	55.8	50.0	76.0	42.0
7	—	66.5	100.0	57.2
Mean	45 % (52.8—34.5)	48.7 % (17.5—68.5)	75.3 % (48 —100.0)	65 % (42.2—96.6)

Generally the countings showed identical values on the two sides but also some asymmetry just as observed clinically was seen (cases 10 14).

In four patients (two without joint complaints and two with RA) I131 tagged fibrinogen was injected into the knee joint in an amount of 50 μ C. Besides countings of the knees plasma samples were examined.

In contrast to the control patients the RA patients showed a higher mean proportion of clot/plasma as seen in table IV. The countings expressed in percentage of the initial countings as shown in fig. 2 showed almost the same decline except for one RA patient. Here the initial decline was somewhat slower whereas the final countings were almost identical in the four cases.

DISCUSSION

The results are within the ranges of those presented by McFarlane (14). The fact that the only difference between the two groups was the total fibrinogen turnover (g/day) may be due to an increased synthesis. This may lead to a higher level of total fibrinogen concentration in the RA patients. The increased mass of fibrinogen catabolized is in some respect unexpected as the fibrinolytic activity is changed and tends to be decreased in patients with RA. On the other hand in his study with dogs Lewis et al. (13) found unchanged turnover rate of fibrinogen even when fibrinolytic activity was stopped by extreme high doses of

— 2

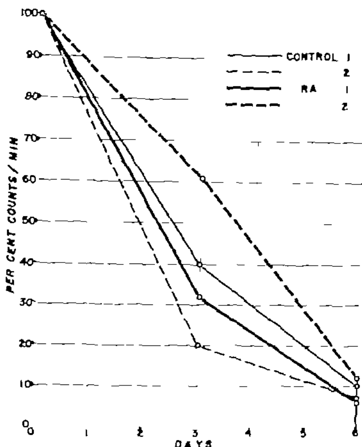


Fig. 2 The countings of the joint after intraarticular I^{131} fibrinogen administration *in two cases with RA and in two cases without joint diseases. The countings* on the third and the sixth day are expressed in percentage of the first counting.

aminocapronic acid (EACA). These findings and the constancy of the *turnover rate independent of patients, point to a more central* or cellular break down of fibrinogen as proposed by Adelson (1). In this connection it is interesting that Lewis found the highest organ radioactive concentration in the lungs.

Focusing the inflamed area as it is found in the joints of RA the increased content of radioactivity in contrast to the controls was evident. That a real increase of fibrinogen in the joint space has taken place, and this even on the first day is in line with other studies. In one

autoradiography and another with I131 tagged antifibrinogen a deposit was demonstrated (9.10). In the last study the antifibrinogen was compared with I131 tagged albumin. In contrast to albumin antifibrinogen was sustained for one week, whereas albumin disappeared rapidly. It was suggested that the presence of the labelled albumin was a measure of increased vascularity in the synovial membrane. In the present experiment with I131 tagged fibrinogen injected into the joint space an almost identical decline in the countings seemed to be determined by different procedures as the relation clot/plasma radioactivity differed in the two groups. In the control group this value was primarily smaller, more constant and without the increase demonstrated in the patients with RA. Earlier studies have illustrated an equal resorption of globulins from joint space in normal persons and in patients with RA (18). In normal synovial fluid plasminogen but no alpha macroglobulin, a specific antiplasmin, has been demonstrated, which is in contrast to rheumatological synovial fluid. This plasminogen may be sufficient to free the normal joint space from fibrinogen in the concentration used here (8). Therefore a local resorption rather than a local lysis in the RA patients is the most probable (in contrast to the control group).

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SJÖGREN'S SYNDROME IN PSORIATIC ARTHRITIS ANKYLOSING SPONDYLITIS AND REITER S SYNDROME

By

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W CARSON DICK GEORGE NUKI and W WATSON BUCHANAN

INTRODUCTION

Sjogren s syndrome is a chronic benign inflammatory disease affecting *the* lacrimal and salivary glands resulting in deficient lacrimation keratoconjunctivitis sicca and salivation causing xerostomia About 60 % of cases are complicated by a connective tissue disease usually rheumatoid arthritis (5) To our knowledge no study of the prevalence of Sjögren s syndrome has yet been made in other chronic arthritides and we therefore considered *it relevant* to investigate patients with Reiter s disease psoriatic arthritis and ankylosing spondylitis for this complication

MATERIALS AND METHODS

Patients Studied

Forty one patients with psoriatic arthritis (15 male 26 female mean age 45 6 years) 26 patients with ankylosing spondylitis (19 male 7 female mean age 42 5 years) and 44 patients with Reiter s disease (mean age 32 5 years) were included in the study Also included were 28 young male patients with rheumatoid arthritis (mean age 32 7 years) to act as

a control group for the patients with Reiter s disease who tended to be younger than our patients with rheumatoid arthritis (RA)

Psoriatic arthritis was diagnosed in patients having the typical cutaneous manifestations of psoriasis together with a seronegative poly arthritis frequently affecting the distal inter phalangeal joints and often having the typical x ray changes Ankylosing spondylitis was diagnosed on the history and typical x ray changes in the sacro iliac joints and apophyseal joints in the vertebral column Reiter s syndrome was diag nosed on the presence of the classical triad of conjunctivitis arthritis and urethritis

Ophthalmological Examination

All patients were screened routinely by an ophthalmologist (J W) for the presence or absence of keratoconjunctivitis sicca A Schirmer I tear test was performed using standard filter paper strips 5 mm wide and folded 5 mm from the end as developed by Halberg and Berens (Contac tisol Ltd Lindenhurst New York) The folded end was placed in the lower eyelid at the junction of the middle and outer thirds After 5 minutes the length of wetting of the filter paper was measured wetting of 15 mm and over was considered normal whereas those with wetting of under 15 mm were subjected to a Schirmer II test This is identical to Schirmer I test but lacrimation was stimulated by a 10 % solution of ammonia held 6 inches from the nose Wetting of the filter paper of over 15 mm in the Schirmer II test was considered normal Patients having deficient lacrimation in the Schirmer II test then had a drop of rose bengal dye instilled into the conjunctival sac and immediately washed out with saline The cornea and conjunctiva were then viewed through a Zeiss or Haag Striett slip lamp for the presence of a punctate or filamentary keratitis Staining in the area of conjunctiva previously in contact with the filter paper was ignored Patients having a diminished Schirmer II test and a punctate or filamentary keratitis were said to have definite keratoconjunctivitis sicca whereas those having only a diminished Schirmer II test were said to have possible kera toconjunctivitis sicca (14)

Oral Examination

Patients were closely questioned for symptoms of xerostomia and the presence of difficulty in mastication and swallowing necessitating increased fluid intake The oral cavity was examined for evidence of

xerostomia especially the absence of a pool of saliva under the tongue Atrophy of the mucous membranes and severe caries were also noted (5)

Salivary Flow Rates

Saliva was collected using a Carlsson Crittenden cup under conditions of lemon juice stimulation as this in our hands has given the most sensitive index of salivary gland secretory capacity

Sialography

Sialograms were performed using the hydrostatic technique of Park and Mason (10) Sialographic abnormalities were based on the criteria of Bloch et al (5)

Biopsy of the minor salivary glands in the lower lip was performed using the technique of Chisholm and Mason (6)

Clinical Features

The presence or absence of Raynaud's phenomenon lymphadenopathy and splenomegaly functional grade (12) and x ray changes were documented as was the articular index (11)

Laboratory Features

Hemoglobin concentration (G/100 ml) white cell and platelet counts (per cu mm) erythrocyte sedimentation rate (mm in the 1st hour — Westergren) and serum albumin and globulin concentration (G/100 ml) were all estimated

Serological Studies

Rheumatoid factor was detected by the latex agglutination technique (Hyland Laboratories) screening the sera at a 1/20 dilution and then testing positive sera by the sensitised sheep cell agglutination test (15) at a dilution of 1/32 and then at doubling dilutions until an end point of agglutination was reached

Antinuclear factor Sera were screened at 1/16 dilution using the indirect immunofluorescence technique of Beck (3) Positive sera were titrated in quadrupling dilutions until an end point of nuclear staining was achieved

Non tissue specific precipitating antibody was detected by Ouchterlony's double diffusion technique in agar gel Sera were tested neat and at a 1/8 dilution using thyrotoxic thyroid gland as substrate (2)

TABLE I

Clinical Features of Patients Studied

Clinical features		Psoriatic arthritis	Ankylosing spondylitis	Reiter's disease	Males < 45 years old with RA
Number		41	26	44	28
Sex		15 M 26 F	19 M 7 F	44 M	28 M
Age (years)	Mean	45.6	42.5	32.5	32.7
	Range	19—78	16—82	17—69	23—47
Duration of disease (years)	Mean	7.6	14.2	5.6	5.7
	Range	2/12—32	2—53	1 week—70 years	4 months—16 years
Kerato conjunctivitis	Possible	2 (4.9%)	1 (3.8%)	0	0
	Definite	4 (9.8%)	0	0	0
Xerostomia	Symptomatic	10 (24.4%)	5 (19.2%)	11 (25%)	2 (7.1%)
	Definite	1 (2.4%)	0	0	0
Salivary gland enlargement		2 (4.9%)	0	0	0
Raynaud's phenomenon		7 (17.1%)	1 (3.8%)	1 (2.3%)	2 (7.1%)
Drug allergy		5 (12.2%)	4 (15.4%)	1 (2.3%)	0

Thyroid Antibodies

Thyroglobulin antibody was detected by the tanned red cell hemagglutination technique (7) sera being initially tested at a 1/16 dilution and positive sera titrated in quadrupling dilutions until the end point was reached. The presence of thyroid microsomal antibody was determined by the indirect immunofluorescence technique (8).

The indirect immunofluorescence technique was also used to detect gastric parietal cell antibody (1).

Salivary Duct Auto Antibody

Submandibular salivary gland was taken within 4 hours of post mortem and snap frozen on metal chucks with CO_2 snow. Sections of 6 μ thickness were cut on a cryostat and test sera placed over the section for 30 minutes. The sections were then washed for 10 minutes in barbitone

TABLE II

Laboratory Features of Patients Studied

Laboratory features	Psoriatic arthritis	Ankylosing spondylitis	Reiter's disease	Males < 45 years old with RA
Number	41	26	44	28
Globulin Mean	3.5	3.4	3.5	3.3
(G/100 ml.) Range	2.1—4.6	2.5—4.5	2.2—4.8	2.0—4.9
RA latex	7/41 (17.1%)	4/26 (15.4%)	5 (11.4%)	23 (82.1%)
Sheep cell agglutination test	1/4 (2.4%)	1/26 (3.8%)	0	22 (78.6%)
Antinuclear factor	4/40 (10.0%)	1/26 (3.8%)	2/43 (4.7%)	2 (7.1%)
Thyroglobulin antibody (Tanned red cells)	1/40 (2.5%)	3/26 (11.5%)	2/43 (4.7%)	0/27 (0%)
Thyroid microsomal antibody	4/40 (10.0%)	4/26 (15.4%)	2/43 (4.7%)	1/27 (3.7%)
Gastric parietal cell antibody	4/40 (10.0%)	3/26 (11.5%)	2/43 (4.7%)	3/27 (11.1%)
Non tissue specific precipitin	0/40	2/26 (7.7%)	0/43	0/27 (0%)
Salivary duct antibody	0/34	1/26 (3.8%)	1/37 (2.7%)	8/18 (44.4%)
Sialographic abnormality	1/26 (3.8%)	1/16 (6.3%)	2/15 (13.3%)	—
Labial biopsy	1/14 (7.1%)	/12 (16.7%)	0/10 (0%)	—

buffer and then fluorescein conjugated rabbit antihuman gammaglobulin was applied for a further 30 minutes followed by another wash in 10 minutes. Sections were mounted in buffered glycerol and viewed under blue light (9).

RESULTS

The clinical and laboratory results of the patients studied are shown in tables I and II.

TABLE III

Clinical and Laboratory Features of Patients with Psoriatic Arthritis and Keratoconjunctivitis Sicca

A Clinical Features

Patient	Age (years)	Sex	Duration disease (years)	K C S	Xerostomia	Salivary gland enlargement	Raynaud's phenomenon	Articular index	Functional grade	X ray changes	Sialogram
1	56	F	4	Definite	Definite	Intermittent	+	78		Loss of joint space in hip joints	Normal
2	58	F	1	Definite	—	—	—	12	2	Pencil and cup changes	Normal
3	56	F	9	Left eye only	—	—	+	[illegible]	3	Erosions + sacroileitis	Normal
4	45	F	8	Definite	Symptomatic	—	—	8	3	Loss of joint space	Normal

B Laboratory Features

Haemoglobin (G/100 ml)	W C C (per cu mm)	Platelets (per cu mm)	E S R	Albumin (G/100 ml)	Globulin (G/100 ml)	RA latex	Sensitized sheep cell agglutination test	Antinuclear factor	Non tissue specific precipitating antibody	Thyroglobulin antibody	Thyroid microsomal antibody	Gastric parietal cell antibody	Salivary duct antibody	Labial biopsy
14.6	8 400	—	37	3.6	3.8	—	—	—	—	—	—	—	—	Focal lymphocytic sialadenitis (Grade III)
13.2	8 400	—	78	3.9	3.9	—	—	—	—	—	—	—	—	not done
13.8	9 600	390 000	85	3.0	4.1	weakly positive	—	1/16 + (homogeneous)	—	—	—	—	—	normal
12.5	6 000	—	67	3.4	3.6	—	—	—	—	1/256	+	+	—	not do

Psoriatic Arthritis

Four patients (9 8%) had definite and two (4 9%) had possible keratoconjunctivitis sicca Patient 1 also had definite xerostomia with intermittent painful salivary gland enlargement allergy to phenobarbitone severe Raynaud s phenomenon and a history of treated thyrotoxicosis Laboratory investigations revealed a normal sialogram, but a diminished lemon juice stimulated salivary flow rate in the left parotid gland (0 4 ml/minute) but a normal flow rate in the right parotid Labial mucosal biopsy revealed a grade III (focal) lymphocytic infiltration of the minor salivary glands

Patients 2 3 and 4 had no other evidence of Sjögren s syndrome apart from keratoconjunctivitis sicca (Table III) Of the 2 patients with possible keratoconjunctivitis sicca one had intermittent salivary gland enlargement but mucosal biopsy sialography and salivary flow rates were all normal One patient a 49 year old female who had had psoriatic arthritis for 12 years and no clinical or laboratory evidence of Sjögren s syndrome had punctate sialectasis on sialography but a normal salivary flow rate (1 40 ml/minute)

The mean salivary flow rate for the group was normal (1 38 ml/minute range 0 40—2 20 ml/minute) and apart from patient 1 all were within the normal range

No other features of Sjögren s syndrome were apparent in this group of patients

Ankylosing Spondylitis

Of the patients with ankylosing spondylitis none had definite clinical evidence of Sjogren s syndrome although one patient did have possible keratoconjunctivitis sicca and symptomatic xerostomia However laboratory data was essentially normal suggesting that this patient did not have a mild subclinical Sjogren s syndrome

The laboratory investigations showed that salivary flow rates were well within the normal range (mean 1 46 ml/minute range 0 75—2 30 ml/minute but one sialogram from a 26 year-old female showed the appearance of atrophy (gross attenuation of the peripheral salivary duct system) and narrowing of the main duct without any other clinical or laboratory evidence of Sjogren s syndrome Salivary duct antibody was found in one patient a 51 year-old female who had typical ankylosing spondylitis on x ray together with an arthropathy affecting the large joints only knees hips elbows and wrists Serological investigation showed that she

was seropositive for rheumatoid factor in a titer of 1/256 She also had grade 3 lymphocytic sialadenitis on labial mucosal biopsy It is probable that this patient has both ankylosing spondylitis and RA As salivary duct antibody (9 13) and focal lymphocytic sialadenitis (6 13) are frequently found in RA this may explain their presence in this patient, but the finding of a grade 3 labial mucosal biopsy in another patient with ankylosing spondylitis a 31 year old male without evidence clinical or serological of Sjogren s syndrome or RA suggests that focal lymphocytic sialadenitis is possibly a feature of ankylosing spondylitis

Reiter's Syndrome

Like patients with ankylosing spondylitis patients with Reiter s syndrome did not have any definite clinical evidence of Sjogren s syndrome This may be because the patients were very young (mean age 32 5 years) as a group of young male patients with RA (mean age 32 7 years) did not have clinical evidence of Sjogren s syndrome either Salivary duct antibody was found in one 40 year old patient with Reiter s syndrome No explanation for this occurrence was obvious from the clinical or laboratory data One point of interest was that the young male rheumatoid arthritics had a very high prevalence of salivary duct antibody (8 of 18 44 4%) which indicates that our suggestion that patients with Reiter s syndrome do not get Sjogren s syndrome because of their youth is probably incorrect Salivary flow rates (mean 1 59 ml/minute range 0 85—2 11 ml/minute) and minor salivary gland histology were normal but sialography revealed 2 patients having definite atrophic changes in their parotid glands and a third having minor changes suggestive of atrophy In none of these patients could we find any explanation for these changes but 2 had mouth ulcers as part of the symptom complex of Reiter s syndrome and it is conceivable that changes in the parotid gland may also have been present

DISCUSSION

In this study we have attempted to see whether Sjögren s syndrome is a complication of psoriatic arthritis ankylosing spondylitis and Reiter s syndrome Only 1 of 41 (2 4%) patients with psoriatic arthritis had Sjögren s syndrome which may be a chance occurrence Four patients including the patient with Sjogren s syndrome had definite

keratoconjunctivitis sicca (9 95%) which is somewhat higher than one would expect in a normal hospital population (Williamson et al 14) who found that 5 of 72 (6 9%) normal females had keratoconjunctivitis sicca, but no data was noted on normal male subjects As all our 4 patients with psoriatic arthritis and keratoconjunctivitis sicca were females and 26 of the group of psoriatic arthritics were females thus gives a prevalence of keratoconjunctivitis sicca in female patients 15 4 % which to us seems very high However, this is not significantly higher than the prevalence noted by Williamson et al (14) as tested by chi square test using Yate s correction for continuity for small numbers Although the results of this study show that Sjögren s syndrome is undoubtedly not a complication of ankylosing spondylitis or Reiter s syndrome we feel that it is possible that a larger study of patients with psoriatic arthritis may reveal a marginally increased prevalence of the disease when compared to a control population We are aware of the possibility that selection bias in hospital patients may be giving falsely high prevalence of kera toconjunctivitis sicca in psoriatic arthritis (4) but feel that this is unlikely as none of the patients at the time of referral were suspected of having this disease

The presence of focal lymphocytic infiltration in the minor salivary glands in 2 cases of ankylosing spondylitis and the infrequent sialo graphic abnormalities in patients in all 3 clinical groups is difficult to explain However focal lymphocytic sialadenitis has been noted in 1 of 10 (10%) of osteoarthritic patients who did not have evidence of Sjögren s syndrome (13) and sialographic abnormalities are not in frequent in normal subjects (14) This evidence suggests that the abnormalities noted on biopsy and sialography may well be fortuitous and therefore support our conclusion that Sjögren s syndrome is probably not a complication of the para rheumatic diseases studied

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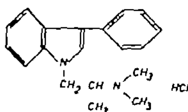
CONTROLLED CLINICAL TRIAL OF 1 (2 METHYL 2 DIMETHYL AMINO ETHYL) 3 PHENYL INDOLE HCl (A28A) IN RHEUMATOID ARTHRITIS COMPARED WITH INDOMETHACIN (CONFORTID[R])

By

LEIF NYFOS

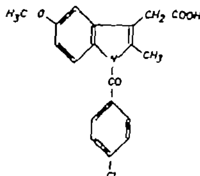
Summary The antirheumatic effect of a new drug A28A, in rheumatoid arthritis proved to be approximately equal to that of indomethacin Side effects were of a similar nature and of approximately the same frequency as with indomethacin In two out of 30 cases transient leukopenia and a transient elevation of the GP transaminase occurred in one case each on A28A The justification of the new drug is seen from the fact that in a number of cases its effect exceeded that of indomethacin.

In 1962 the Dumex laboratories synthetized a substance 1 (2 methyl 2 dimethyl amino-ethyl) 3 phenyl indole HCl (A28A) which in animal experiments showed not only an analgesic effect but also an antiphlogistic action 2—3 times that of phenylbutazone The preparation was therefore of interest as an antirheumatic agent However clinical trial in man was only sporadic in 1962 Instead it was endeavoured to spread knowledge about indomethacin in rheumatic diseases as this agent appeared to be fairly non toxic and to possess a definite antirheumatic effect Empirically however indomethacin has given rise to side effects in numerous cases so that the new substance (A28A) might become an alternative possibility depending upon its effects and side-effects in man



2 m thyl 2 d m thyl m ethyl) 3 phenyl ndol HCl

(A 28 A)



INDOMETHACIN

Fig 1

In collaboration with the makers Dumex Ltd we have performed a double blind trial by a cross-over technique (A28A/indomethacin) on 30 patients with rheumatoid arthritis in the Hospital for Rheumatic Diseases Skælskør during the period May 1968 to January 1969

The drug is a phenyl indole compound having the formula shown in fig 1 Its molecular weight is 314 9 In animal experiments its acute toxicity on oral administration has been found to be much lower than that of indomethacin the LD_{50} in rats being 700 mg/kg and in mice 410 mg/kg whereas for indomethacin the LD_{50} is 12 mg/kg and 50 mg/kg respectively Chronic toxicity studies have been performed on rats and no organ changes were observed on a dosage of 50 mg/kg daily for 10 months

Antiphlogistic experiments with inhibition of erythema in guinea pigs had demonstrated a more potent action than obtained with phenylbutazone and the cotton pellet test and effect comparable to that of phenylbutazone In the paw edema test the effect was the same as with indomethacin while the test using incorporation of radioactive ^{35}S in the cartilage (chondroitin sulphuric acid) showed A28A to be more potent than indomethacin In addition A28A had a distinct effect upon the temperature center corresponding to that of chlorpromazine, and an analgesic effect midway between that of codeine phosphate and amidopyrine

A clinical trial has been carried out only on a couple of series in 1962 in the Physical Medicine Department of the Glostrup Hospital Copenhagen

In one of these trials the drug was compared double blind with placebo in 11 patients with RA (3) A distinct anti inflammatory action was obtained and as for side effects only mild transient dyspepsia occurred in three patients The other trial (1) comprises a material composed of 43 patients with osteo-arthritis and five with RA In this series a satisfactory effect was obtained in 50 % while various side effects occurred in about 40 % In a number of cases A28A was found to be better than phenylbutazone

METHOD

The present trial was carried out at the Hospital for Rheumatic Diseases Skelskor Denmark where the patients usually stay for about three months Accordingly a double blind trial may be carried out over a sufficiently long time on in patients who are checked daily The trial was planned as a double blind experiment by an extended cross over technique continued for nine weeks divided into three successive 3 week periods The patients received identical looking capsules having different independent code numbers The two drugs were administered as follows *Period A (first 3 weeks)* period *B* (next 3 weeks) and period C (last 3 weeks) The capsules during the last 3 weeks (C) were always the same as during the first 3 weeks (A) The coding had been made so that half the patients started on A28A while the other half started on indomethacin* Each capsule contained 25 mg either of

* Marketed as Confortid® capsules by Dumex Ltd

— 8

TABLE I

Index Numbers for Grip Strength, Walking Test and for Changes of the Circumference of Joints

Grip strength kp/cm	%	Walking test seconds/15m	%	Changes of circumferences of joint	
1 45—1 50	0	10—12	0	+ 2½ cm	20
1 40—1 45	1	13—15	1	+ 2	18
1 35—1 40	2	16—18	2		
				0	10
0 05—0 10	28	79—81	23	—	
0 —0 05	29	82—84	24	— 2½	0
0	30	85—87	25		

A28A or of indomethacin and the daily dose was 75 mg administered in three divided doses. The trial was started when the nature of the disease had been confirmed by clinical and laboratory investigation, i.e. after about 7—14 days in hospital.

In analysing the therapeutic results it is very important to obtain a numerical expression of the various parameters which may give rise to alterations in the disease activity, whether it refers to subjective or objective criteria. Since the subjective and objective parameters do not always show parallel changes during the course of a treatment, it would appear suitable to add up the parameters of an activity index suggested by Lansbury in 1958 (4). However, I used a modified activity index in order to incorporate a couple of more objective criteria. The higher the value in this index, the greater the disease activity and the larger the number of involved joints, while an improvement manifests itself as a fall of the index.

The original Lansbury index uses the following parameters: 1. Morning stiffness. 2. Time of onset of fatigue. 3. Need for aspirin. 4. Grip strength. 5. Erythrocyte sedimentation rate. 6. Joint index. In my modification of this index, item 2 is replaced by measurement of the circumference of the interphalangeal joints of the index and middle finger of both hands and item 3 by walking test (walking time for

TABLE II

Age Distribution

Age	Num
30—39	
40—49	5
50—59	
60—69	6
70—74	

the distance 15 m) Analysis of the various parameters is done at the institution of the trial i e after 7—14 days clinical and laboratory observation and at the end of each treatment period The code for the capsules was not opened until the entire trial had been completed and the various parameters had been recorded

Together with the clinical parameters we also recorded weight Hb white blood count serum creatinine and GP transaminase Moreover the urine was studied for protein and sugar and the feces for benzidine reaction

MATERIAL

Of the 30 patients 20 were females and 10 males According to Steinbrocker's staging (7) 19 were in stages I—II and 11 in stages II—III As far as the ARA criteria of RA are concerned 14 were classical cases 15 definite and 1 in the group probable Table II gives the age distribution

The material was divided into 2 groups (I and II) group I comprising patients who received A28A during periods A and C (first and last 3 weeks) while group II comprises patients who received indomethacin during periods A and C During the B period (middle 3 weeks) the patients received the other drug for comparison

Out of 30 patients 7 received prednisone in a dosage of 2 5—7 5 mg daily throughout the treatment period and 4 received Myocrisin or Sanocrysin during the treatment period In addition the patients were given the necessary analgesic supplement in the form of acetylsalicylic acid

TABLE III

Activity Index

Group I

No	Before	A28A	Indomethacin	A28A	Average A28A
1	77	75	52	62	62
4	65	58	60	67	62
6	79	77	77	71	71
7	98	92	97	102	97
9	74	69	65	63	66
12	87	93	87	92	92
14	48	49	45	57	55
15	119	109	94	91	100
17	103	87	81	81	84
20	53	41	40	38	39
22	80	81	74	77	79
23	95	82	84	91	86
25	95	76	74	66	71
28	92	90	85	100	95
29	86	92	89	87	89

Three patients had no consumption of acetylsalicylic acid during the trial while the other 27 patients had permanent or changing intake of acetylsalicylic acid Comparing the consumption during treatment with A28A and indomethacin two patients had increased analgetic demand in the A28A period, whereas two other patients had increased demand in the indomethacin period

RESULTS

Tables III and IV present the activity index for group I and group II separately at the institution of the trial and at the end of periods A—C

On comparison of the indices at the institution and after the completion of treatment with A28A in group I calculation by the t test showed a significant reduction of the activity index after A28A within the 95 % limit ($0.02 < P < 0.05$) In group I however the effect of indomethacin was better ($0.02 < P < 0.05$)

TABLE IV

Activity Index

Group II

No	Before	Indomethacin	A28A	Indomethacin	Average Indomethacin
	79	discont	78	—	—
3	78	66	83	79	72
5	121	119	101	96	107
8	78	52	59	68	60
10	61	59	50	50	54
11	126	105	141	119	112
13	80	64	65	67	65
16	59	44	40	40	42
18	59	62	56	61	61
19	78	79	70	72	75
21	109	108	104	104	106
24	93	94	107	116	105
6	87	88	86	97	92
27	101	86	87	83	84
30	85	89	85	67	78

Within group II the t test showed an effect of indomethacin within the 95 % limit (0 01 < P < 0 02) A comparison of A28A with indomethacin group II shows no significant difference between the effect of the two substances (0 6 < P < 0 5)

Assuming that a reduction of the activity index of 2 points indicates an improvement from the initial situation and that an alteration of 2 points shows a difference in the effect of the two substances an effect of A28A was found in 19 out of 29 cases while indomethacin was effective in 23 out of 29 cases The effect of both substances was the same in 4 cases while A28A was superior to indomethacin in 8 cases whereas indomethacin was more effective than A28A in 12 cases

Laboratory Tests

Recording of changes in body weight comparing with the initial value and using for periods A and C the mean value showed for group I an average weight gain of 0 23 kg on A28A and of 0 33 kg on indomethacin while in group II the weight changes were minus 0 10 kg on A28A and plus 0 12 kg on indomethacin

TABLE V
Side Effects

	A28A	Indomethacin
No side effects	15	15
Dyspepsia	7	8
Headache nausea	1	2
Dizziness headache	1	1
Edema tendency	4	4
Exanthema	1	—
Itching	1	—
Leukopenia	1	—
Elevated GP transaminase	1	—
Discontinuation of the medication (after 14 days)	1 (itching)	
(after 2 days)		1 (vomiting — headache)

The Hb levels showed changes of only an average of 0 06 g/100 ml and 0 09 g/100 ml on A28A and indomethacin respectively

Leukopenia occurred in one patient on A28A In case 15 the white blood count during period A on A28A was 4 200 after an initial count of 4 000 This did not change during period B on indomethacin but during period C when A28A was administered again the count fell to 2 000 Regrettably further counts have not been performed

Serum creatinine was elevated prior to the treatment in only one case and there was no instance of changes in this value during the experimental periods

As a test of liver function the GP transaminase was checked The normal value is below or equal to 15 mU/ml Case 10 showed an increase from the normal level up to 43 during period B on A28A but at the end of the indomethacin therapy during period C the level was normal again Changes in GP transaminase did not occur in other cases

Furthermore investigation for occult blood in the feces was done by the benzidine reaction The test was negative in 21 cases on both drugs A questionable reaction (+) was observed in 5 and 1 case on A28A and indomethacin respectively while a positive reaction occurred in 3 and 7 cases on A28A and indomethacin respectively The positive benzidine reactions may perhaps be due to irritation of the gastric mucosa

by the simultaneous acetylsalicylic acid medication At any rate there have been no findings of an ulcerogenic effect of A28A exceeding that of indomethacin

Side Effects

The side effects are listed in table V It will be seen that the nature and frequency of the side effect were the same with both drugs and the discontinuation of the medication was needed in only two cases one on each drug However one case of leukopenia occurred on A28A and in another case the same drug gave rise to an elevated GP transaminase value

DISCUSSION

The present investigation was a double blind trial comparing the effect of A28A against one of the better known and more widely used antirheumatics indomethacin This must be considered more useful than comparison with placebo since it must be the quantitative antirheumatic effect as well as the number and nature of side effects which are to be assessed for a new antirheumatic agent compared with other similar drugs with a view to its clinical use

Therefore I modified Lansbury's index in a way so that it still contains six parameters but replaced the somewhat uncertain parameters by recording the circumference of joints and walking speed The use of this modified activity index appears to be fully applicable in a comparison of the effect of two drugs in a double blind trial and considerably facilitates the statistical analysis

However the incorporation of Lansbury's joint index in the activity index used carries the disadvantage that normalization of a few of the small joints (fingers or toes) does not manifest itself in the index

In the *present trial there* was a demonstrable effect of A28A within the 95 % limit and in *one* of the experimental groups the effect of A28A was *identical* with that of indomethacin (15 patients) while the other 15 patients showed a somewhat better effect of indomethacin However the striking value of a drug like A28A may be seen when considering that in 8 cases its effect exceeded that of indomethacin In another 12 cases however indomethacin was more effective than A28A

In respect to side effects the incidence was very much alike with both drugs and so was the nature of the side effects as regards mild dyspepsia and a slight tendency to edema However one patient exhibited leukopenia and one an elevated GP transaminase on A28A but both were transient and soon subsided These two patients were not receiving chrysotherapy at the same time or other drugs known to influence the blood cells or liver function

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FEMORAL NECK FRACTURE OF THE RHEUMATOID HIP JOINT

A Study of 20 Operatively Treated Cases

By

VEIJO VAHVANEN

Summary The series comprises only patients with rheumatoid arthritis admitted for treatment because of femoral neck fracture. The total number of 20 cases on 19 patients were classified into the following groups

1 Fractures of the femoral neck (13 patients) In two cases the fracture was spontaneous The fracture was treated by replacement of the femoral head with an endoprosthesis (Moore or Thompson) in seven instances and by nailing in seven instances One patient had a femoral neck fracture twice (the opposite hip) at an interval of seven years The follow up results were good or fair in nine cases poor in three Two cases were omitted because of the very short follow up time

2 Pertrochanteric fractures of the femur 6 patients. All these cases were treated by nailing with the fixed angle nail One pseudarthrosis developed

INTRODUCTION

Fracture of the upper femur is a particular problem in the rheumatoid patients Because of marked osteoporosis caused by the rheumatoid inflammation and inactivity even a slight injury may lead to fracture, or spontaneous femoral neck fracture may occur Demartini et al (6) stated that spontaneous femoral neck fractures (FNF) however are very infrequent in patients with rheumatoid arthritis (RA) treated with

TABLE I

Distribution of the Material According to Duration of RA

(Interval in years between the onset of symptoms of RA and operation)

Group	1—5	6—10	11—15	>15	No of operations
Femoral neck fracture (FNF)					
Nailing	3	1	2	1	7
Endoprosthesis	1	3	2	1	7
Pertrochanteric fracture (PF)					
Nailing	1	2	1	2	6
Total	5	6	5	4	20

cortisone According to these authors spontaneous fractures of the vertebral bodies are much more common Werne (14) and Reichelt (11) described two patients with RA treated with cortisone who showed spontaneous fracture of the femoral head or neck No extensive follow up series of FNF in patients with RA have been published In this paper mention is made of the healing process and operative therapy of femoral neck fractures in rheumatoid patients

MATERIAL

The present series consists only of patients with RA admitted for treatment because of femoral neck or pertrochanteric fracture (FNF PF) The operations were performed at the Department of Orthopedics and Traumatology University Central Hospital Helsinki during the years 1962—1969 The total of 20 cases on 19 patients were classified into duration groups as indicated in table I The duration of RA was most frequently over five years Of the patients 18 were female and only one male In this case the disease resembled spondylarthritis ankylopoietica while the remaining cases were diagnosed as definite RA (12) Left and right sided cases were equally numerous except in the second group There were five pertrochanteric fractures on the left side and one on the right side The patients could not clearly recall the onset of the first

TABLE II

The Operative Methods

Operative method	No of cases
Nailing (FNF)	
Smith Petersen	6
McLaughlin s nail anchored with one screw without shaft	1
Fixed angle nail (PF)	
Barnes	6
Endoprosthesis	
Austin Moore	6
Thompson with cement	1
Total	20

symptoms in the hip joint Mostly they had experienced pain from time to time for many years





Plate 1 A *Plate 1 B*

1 A Pertrochanteric fracture in a 60 year old woman with symptoms of RA for over 20 years Marked narrowing of the joint space

1 B Six years later No progression of RA in the hip joint The flexion of the joint is 100 degrees and the joint was painless The patient used one stick because of the destruction of the knee joint.

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Plat 2 A *Plate 2 B*

A Femor l neck fracture in a 49 year old patient who had suffered from RA for over 1 years

2 B The f cture was nailed 12 days after injury Satisfactory reduction

For operative methods see table II Only one femoral head was dislocated into valgus position the remaining cases were dislocated into varus At the time of operation the age of the patients with FNF ranged

TABLE III

The Follow up Periods in Years in the Different Operative Groups

Group	<1	1—2	3—4	5—6	7—8	Total
FNF						
Nailing	2	0	1	3	1	7
Endoprosthesis	1	2	1	0	1	5
PF						
Nailing	0	2	1	3	0	6
Total	3	4	3	6	2	18



Plat 2 C *Plat 2 D*

2 C Three and a half months later the nail has slipped out. Non union
2 D The femoral head was replaced by Moore's endoprosthesis within six months from the primary operation The condition nearly two years later No loosening of the prosthesis fair result

from 47 to 79 years the mean age being 66 years The age of the patients with PT ranged from 32 to 72 years the average being 57 years

The x ray findings in the hip joint were slight (Plate 1) and consisted mainly of moderate or severe osteoporosis and slight osteoarthrotic changes

Mechanism of Injury

Six patients had tumbled at home and seven patients just outside their homes Three patients used two walking sticks when the accident occurred Four patients sustained fracture when tumbling in a bus driving a bicycle or being overturned by a car In *two* cases there was no trauma These patients had experienced continuous pain in the hip for some length of time On getting up from a chair by the aid of a stick they experienced acute severe pain Spontaneous femoral neck fracture was diagnosed in both cases One patient had an accident at home twice at



Plate 3 A



Plate 3 B

3 A Fracture of the femoral neck in a 47 year old patient with symptoms of RA for two years
3 B The condition after the fixation with Smith Petersen s nail

an interval of seven years which makes altogether 20 cases of FNF The ages of the patients with spontaneous FNF were 76 and 67 years and they had suffered from RA for 10 and 15 years respectively The older patient had used cortisone for two years prior to the fracture In both cases severe osteoporosis was present

TABLE IV

End Results in 18 Cases Followed up

Group	Good	Fair	Poor	Total
FNF				
Nailing	4	0	3	7
Endoprosthesis	1	4	0	5
PF				
Nailing	5	0	1	6
Total	10	4	4	18



Plat 3 C



Plat 3 D

3 *C* Three years later Avascular necrosis f the femoral head and destructive changes in the acetabulum The nail has been removed

3 *D* The condition fter the arthrodesis Union occurred and the hip was painless at the follow up

Follow up Studies

Follow up examinations were performed by the author personally in 10 patients and in 7 cases by the aid of questionnaires answered by the patients or their relatives At the time of writing 9 of the 19 patients had died Two patients died within four months from the operation (Moore s endoprosthesis) of cardiovascular failure These patients were omitted from the follow up study The follow up periods in the different operative groups appear in table III The average follow up time was 3 8 years The follow up examinations were performed in the year 1970

The *end results* are shown in table IV FNF was treated in our hospital with Smith Petersen s nail in six instances and in one instance with McLaughlin s nail anchored with one screw without shaft Four of these



Plate 4 4 Pertrochanteric f cture in a 52 year old woman with RA of eight years duration N destructiv changes in the joint

cases were successful and three were failures In one case of FNF treated with Smith Petersen s nail the nail loosened within four months and there was painful non union of the fracture The case was successfully reoperated and the femoral head was replaced by Moore s endoprosthesis (10) plate 2 In two cases of FNF avascular necrosis of the femoral head developed Both fractures were fixed by Smith Petersen s nail One of these patients was later treated by arthrodesis of the hip joint, after which the hip became painless plate 3

The treatment of PF with the fixed angle nail was successful in five cases while pseudarthrosis developed in one case All four screws fixing the angle nail of Barnes were found to be broken within six months from the operation and the nail had loosened Painful pseudarthrosis was present

The results were good or fair in five cases of FNT treated by en doprosthesis There were no failures At the time of operation four patients were over 70 years old The indications of the replacement of



Plate 4 B



Plate 4 C

4 B Four months after osteosynthesis with fixed angle nail Union has occurred and the fracture line can hardly be noticed

4 C Six years after osteosynthesis The nail had been removed three years before because of loosening Severe progression of the rheumatoid changes in the hip joint with central depression of the acetabular floor Motion is still satisfactory with flexion of 110 degrees The patient used crutches because of painful knee joint

the femoral head by endoprosthesis were severe RA in an old patient with restricted independence and walking capacity severe osteoporosis and dislocation of fracture Two of these four patients died within four months from the operation and were omitted from the follow up study In two patients the indication of the femoral endoprosthesis was non union and beginning necrosis of the femoral head after the nail fixation of Smith Petersen In one case the FNF was old and there was incipient necrosis of the femoral head This case was treated with Thompson s endoprosthesis (13) with cement Loosening of Moore s endoprosthesis was clinically and roentgenologically suspected in one case but the

patient was still satisfied with the operative result after eight years from the operation

The functional capacity of the patients had deteriorated which was due to rheumatoid progression in other joints Marked progression in the hip joint was radiologically observed in two instances (Plate 4) but the decrease in degree of independence was mainly due to the involvement of other joints (other hip knee or ankle) In 16 of the 19 patients no walking aids were required before the accident, or one stick was used occasionally At the time of the follow up examination nine patients managed without a stick or used it occasionally Four patients used crutches and four patients were confined to bed or wheel chair

DISCUSSION

Treatment of femoral neck fracture by nailing was unsuccessful in three cases In two of these RA had developed gradually for one and two years preoperatively but after the trauma, progression was very rapid and led to destruction in the ankle and knee joints as well as in the injured hip joint Probably the coincidence of trauma and exacerbation of RA in conjunction with dislocation of the primary fracture impaired the prospects of healing

The patients in question were relatively young 47 and 61 respectively and only slight osteoporosis was present at the time of the treatment In the third case RA had set in about 12 years before the accident and marked osteoporosis and narrowing of the joint space were present preoperatively

There was one poor result (pseudarthrosis) in the group of pertrochanteric fracture This was probably due to technical operative failure In all these cases the fixed angle nail of Barnes type was used Despite the progression of RA fusion was successful provided that the fixation was stable

Two patients aged 76 and 67 showed spontaneous femoral neck fracture In both cases severe osteoporosis was present The older patient was treated ad modum Moore s endoprosthesis In the younger patient the fracture was fixed with McLaughlin s nail anchored with one screw and healing occurred within less than six months

In this study Moore s prosthesis was fixed by filling of the holes of the neck with cancellous bone from the femoral head Thompson s en

doprosthesis was fixed with cement The problems are osteoporosis and the possible loosening of the prosthesis or caving in of the acetabular floor When the osteoporotic spongy bone is removed and the cavity of the upper femur is filled with cement round the prosthesis the latter is likely to resist the loosening effect of RA for a longer period The favourable properties of cement were discovered by Charnley (4) and this method was compared to the uncemented series by Follacci and Charnley (7) Avascular necrosis of the femoral head after the failure of nailing can be satisfactorily treated ad modum Moore s or Thompson s arthroplasty particularly in the early stages before the acetabulum becomes involved It is a valuable operation for some cases of recent fracture of the femoral neck accompanied by severe dislocation in old patients (1 2 3 5 8 9)

Conclusions

1 The general opinion that femoral neck fracture appears rather seldom in the patient with an osteoarthrotic hip joint, is supported by this study

2 Femoral neck fracture fixed with Smith Petersen s nail did not heal satisfactorily This was due to the instable method of fixation in conjunction with the osteoporosis and thin cortex of bone associated with RA to the impaired blood supply of the femoral head resulting from the marked dislocation and type of the fracture

3 If the blood supply of the femoral head is not damaged and reduction of the fracture is good a femoral neck fracture probably fuses if the fixation is stable (angle nail)

4 Trochanteric fractures properly fixed with the angle nail of Barnes fused well

5 If the blood supply of the femoral head seems to be poor or severed if the fracture is not fresh or destruction of the femoral head is present it is advisable to replace the femoral head by an endoprosthesis fixed with cement but destructive changes of the acetabulum or caving in of the acetabular floor must not be present

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SYSTEMIC LUPUS ERYTHEMATOSUS INDUCED BY PSYCHOTROPIC DRUGS

By

A J M Fabius and W K Gaulhofer

Summary In two mental hospitals with a total population of 1 800 and an annual turnover of some 500 patients ten cases of symptom poor possible systemic lupus erythematosus were observed in the course of five years. In eight of these cases it was demonstrated that the syndrome was in all likelihood induced by phenothiazines

During medication with the antihypertensive hydralazine 8—12 % of patients develop a clinical picture known as hydralazine syndrome which is clinically indistinguishable from systemic lupus erythematosus (SLE) with which it is probably identical It is characterized by serological changes (positive LE cell test antinuclear factors) and involvement of several organ systems (e g joints serous membranes lungs liver spleen CNS) Its symptomatology is usually less rich than that of spontaneous SLE It is sometimes recognizable solely by the presence of antinuclear factors and/or a positive LE cell test

Since the SLE syndrome following hydralazine medication was first described in 1954 it has been found that a similar syndrome occurs as frequently in association with procainamide medication SLE syndromes or positive antinuclear factors (ANF) as isolated findings can occur in association with administration of the following drugs

Antiepileptics (hydantoin derivatives succinimides primidone trimethadione) tuberculostatics (INH PAS streptomycin) antibiotics

(penicillin and tetracycline) sulpha drugs thyrostatics (methylthiouracil and propylthiouracil) antihypertensives (reserpine, methyldopa, chlortalidone (5)) griseofulvin and phenylbutazone

In 1969 the oral contraceptives were added to this list (2)

The prognosis of the drug induced SLE syndrome fortunately proves to be more favourable than that of the spontaneous SLE Most cases show improvement after discontinuation of the inducing drug Unfortunately however this is not always the case It may take months or years before all clinical manifestations disappear and the LE cell test becomes negative ANF can remain demonstrable up to 9 years after discontinuation of the inducing drug (3)

There are cases which show flare ups and a progressive course even though the offensive drugs are not re introduced

Partly on the basis of a study of SLE case histories of 13 New York hospitals Lee et al (8) assumed that 1 % of the USA population are vulnerable to SLE that is to say have a SLE diathesis The SLE predisposition it is believed can become clinically manifest in response to certain endogenous or exogenous factors such as infection pregnancy excessive exposure to sunlight and administration of drugs

If the SLE diathesis is indeed so common one would expect to encounter cases of SLE in mental hospitals where many patients receive psychotropic medication for months or years

From the literature and from a personal communication we know of two cases of SLE induced by psychotropic drugs Hald (6) and van der Plas (9) each saw a woman who developed the SLE syndrome during medication with chlorprothixene There are also reports on cases induced by reserpine Berglund et al (1) found a positive ANF test *in 46 of 177 women treated with chlorpromazine but none showed* SLE

In 1965 in one of our hospitals the death occurred of a 55 year old woman with leucocytopenia and thrombocytopenia in whom SLE had been clinically diagnosed She had been treated for hypertension *for many years* with reserpine diuretics and various sedatives (e g barbiturates paraldehyde and chloralhydrate) The SLE diagnosis was confirmed at the postmortem

In the two hospitals in which we work we have since made a special search for LE cells and ANF especially in patients under psychotropic medication and suffering from leucocytopenia or thrombocytopenia or showing rheumatic manifestations (arthralgia arthritis tendinitis)

TABLE I

ANF and LE Cells Serological Study of 74 Psychiatric Patients

Indications for study	Number	ANF	LE cell test class IV or V
Rheumatic manifestations	14[1]	5[1]	5[1]
Leucocytopenia, thrombocytopenia	35	7	4
Various reasons	25	0	1[2]
Total	74	12	10

One patient as far as we know had not received any psychotropic drug
[2]In this patient the ANF test was dubiously positive

PATIENTS AND METHODS

The immunological determinations were made at the Central Lab oratory of the Blood Transfusion Service of the Netherland Red Cross in Amsterdam (Director Prof Dr J J van Loghem) The ANF were determined by the immunofluorescence technique The LE cell test was carried out according to Zimmer Hargraves its results were recorded as follows Class III (occurrence of detached amorphous masses) class IV (nuclear phagocytosis) class Va (a few typical LE cells) class Vb (many typical LE cells) Syphilis reactions were carried out at the National Institute of Public Health Utrecht Apart from a few deter minations made in 1965 platelet counts were made in a counting cham ber according to Feissly

A total of 74 cases were serologically examined 10 showed a class IV or V LE cell test and 12 had a positive ANF test (table I)

In one patient a 50 year old woman with rheumatoid arthritis the LE test was positive immediately at admission before we had given any psychotropic medication In 13 other patients with *rheumatic signs or symptoms* we found 4 with ANF and a class IV or V LE cell test Their case histories follow

Patient A the only man in the series born in 1937 had been under treatment for schizophrenia since 1957 In August 1965 our advice was asked in view of recurrent tendinitis of the Achilles tendons General examination disclosed no arthritis or other abnormalities ESR 49 mm leucocyte count 4 850 with normal differential count platelets 210 000 Hb 12 3 g/100 ml ANF positive and LE cell test class Va AST 350 U Syphilis reaction negative Uric acid 3 6 mg/100 ml

The patient had been treated for five years with orphenadrine and the phenothiazine derivate perazine. In July 1966 this was replaced by perphenazine and in February 1968 by thiothixene. At examination in April 1969 the ANF and LE cell tests were still positive (class Va) and anti DNA antibodies were found. Creatinine clearance was undisturbed. No albuminuria. ESR 11 mm. No further symptoms of tendinitis. In September 1969 the LE cell test was for the first time in class III while the ANF test was dubiously positive. In January 1970 the LE class was Va again and the ANF weakly positive.

Patient B, a woman aged 45, was seen as an out patient early in 1969 after 24 months of medication with amitriptyline, promethazine and chlorpromazine to combat phobic symptoms. She had a 4 week history of arthritic symptoms with some symmetrical swelling of the metacarpophalangeal and proximal interphalangeal joints. Head, neck, heart and lungs were normal. Liver and spleen were not palpable. No enlarged lymph glands and no rheumatic nodules were present. Laboratory findings: ESR 7 mm, leucocyte count 5 950 with 45 % segmented cells, platelet count 483 000, Hb 14.1 g/100 ml, Creatinine 7.8 mg/l, Rose test repeatedly negative, ANF positive, LE cell test class Va, Uric acid 3.7 mg/100 ml. Urine no albumin, no hematuria. Syphilis tests negative. No radiological changes suggestive of rheumatoid arthritis.

After this examination chlorpromazine was discontinued. Eight months later when we saw her again the arthritis had disappeared. ANF dubiously positive. LE cell test class IV.

Patient C, a woman born in 1912, had been treated for schizophrenia since 1955 with chlorpromazine (until 1966), reserpine (until 1966), orphenadrine (until now) and barbiturates (until now). In addition she had received levomepromazine since 1960. In 1966 chlorpromazine was replaced by triflupromazine and in 1968 perphenazine was substituted for triflupromazine and levomepromazine. Polyarthritis occurred in 1965. There were no signs of rheumatoid arthritis, rheumatic fever or gout. ESR 53 mm, leucocyte count 8 000, ANF positive, LE cell test at first class III, later class IV. Syphilis tests negative. During salicylate medication the polyarthritis disappeared and the ESR was normalized. In March 1970 the LE cell test was class Va and the ANF was dubious. Perphenazine was then replaced by haloperidol. In September 1970 the LE cell test had diminished to class III with a dubiously positive ANF test.

Patient D a schizophrenic woman born in 1907 had been receiving chlorpromazine and rescinnamine since 1959 ANF were demonstrated in the serum in 1966 at that time the LE cell test was class III ESR 15 mm leucocyte count 5 400 Rescinnamine and chlorpromazine were replaced by levomepromazine In June 1969 periarticular swelling occurred at the metacarpophalangeal joints ESR 42 mm leucocyte count 6 000 platelet count 182 000 Hb 12 7 g/100 ml Rose test negative ANF positive LE cell test class IV Syphilis tests Kolmer test anti complementary VDRL negative AST 100 U Urine no albumin and normal sediment X ray of hand skeleton no ulcerations but periarticular osteoporosis

Levomepromazine was discontinued in September 1969 In December 1969 there were no longer any arthritic symptoms the ESR was 22 mm In March 1970 the ANF and LE cell tests were negative

In 55 patients a serological examination was made in view of *leucocytopenia and/or thrombocytopenia* ANF were found in seven and a dubiously positive ANF test was found in three In four of the seven ANF positive patients the LE cell test was class IV or V The case histories of these four patients follow

Patient E a woman born in 1943 was hospitalized in 1968 with severe phobic symptoms (10 years after hematomyelia had been treated by decompression) Since 1965 she had been receiving various analgesics and psychotropic drugs e g chlordiazepoxide The medication during the six months prior to hospitalization had been a barbiturate and a combination of amitriptyline and perphenazine She was seen by one of us in view of leucocytopenia Head neck heart and lungs were normal Liver and spleen were not enlarged There were no signs of arthritis Laboratory findings ESR 15 mm Hb 13 7 g/100 ml leucocyte count 2 950 with 37 % segmented cells platelet count 248 000 ANF and LE cell tests positive (class Va) Syphilis tests negative Rose test negative Urine no albumin and normal sediment Creatinine clearance 127 ml/min

Eight months after discontinuation of the medication (January 1969) the leucocytopenia was gone (4 300 5 500) and the ESR was 7 mm ANF still present LE cell test class IV

Patient F a woman born in 1895 was under hospital treatment for schizophrenia since 1924 She had received chlorpromazine since 1957 with rescinnamine and orphenadrine added since 1961 In 1965 a medical

examination for low back pain disclosed vertebral osteoporosis Heart, lungs liver and spleen were normal Laboratory findings ESR 80 mm leucocyte count repeatedly < 3 000 without relative neutropenia platelets repeatedly over 100 000 Hb 15 1 g/100 ml ANF and LE cell test positive (class Va) Syphilis tests negative Urine a trace of albumin Medication was continued unchanged until December 1967 from that time until spring of 1969 the only medication was thioridazine The ESR remained high (74 mm) ANF and LE cell tests positive (class IV) leucocyte count repeatedly < 3 000 with normal percentage of neutrophils platelet count normal An attempt to switch to chlorprothixene produced an allergic skin reaction as ampicillin had done a few months earlier In March 1969 the thioridazine was discontinued and replaced by haloperidol The leucocyte count has since remained above 3 000 The ESR diminished to 19 mm The ANF test was dubious and the LE cell test was repeatedly only class III

Patient G a woman born in 1904 was given chlorpromazine rescinnamine and promethazine in 1960 for schizophrenia In May 1966 a routine check up of the patient (who felt well) disclosed leucocytopenia (varying between 1 500 and 4 200) with normal differential count ESR 31 mm Hb 11 4 g/100 ml ANF positive LE cell test class III later class IV This prompted discontinuation of chlorpromazine Unfortunately another leucocyte count was not made until February 1969 It was 1 000 and a few days later 1 000 and 1 800 with normal percentages of neutrophils Platelet counts repeatedly < 50 000 LE cell test class III Syphilis tests negative Urine trace of albumin Physical examination of the asymptomatic patient again yielded nothing remarkable specifically no subcutaneous hematomas Prednisolone medication was started and rescinnamine and promethazine were replaced first by reserpine and later by haloperidol The leucocyte count then rose to > 3 000 and the platelet count to > 50 000 (90 000 54 000 62 000 56 000) ANF dubious LE cell test first class IV and then class III

Patient H (figure 1) a woman born in 1902 was treated for latent syphilis in 1924 *She was hospitalized with schizophrenia in 1939* and since 1957 had been receiving chlorpromazine temporarily supplemented with or replaced by triflupromazine levomepromazine or a barbiturate In September 1964, low leucocyte counts were found In 1964 and 1965 *there were several infections* (pneumonia on four occasions parotitis, a nasal furuncle) In January 1965 the ANF test was positive and the LE cell test was class III The spleen was palpable
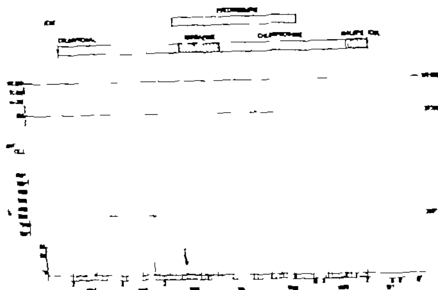


Fig 1 Labor tory data on patient H during treatment with various drugs over the period 1964—1970

April 1966 manifestation of a hemorrhagic diathesis with nosebleeds and large subcutaneous hematomas found to be based on thrombo cytopenia (platelet count 4 000 Fonio) ESR 80 mm leucocyte count 1 900 with normal percentage of neutrophils Hb 13 0 g/100 ml ANF positive LE cell test class IV Syphilis test Kolmer 1 20 VDRL pos itive Treponema pallidum immob test negative Reiter s protein com plement fixation negative Urine no albumin Prednisolone was given at a daily dosage of 4 x 5 mg As the figure shows this had little effect The hemorrhagic diathesis persisted the ESR remained high and the platelet count low only the leucocyte count increased Chlorpromazine as a probable inducer of the syndrome regarded as SLE was replaced by thioridazine The ESR then diminished leucocyte counts were repeat edly > 5 000 and the hemorrhages ceased Because the platelets showed an insufficient response the phenothiazine derivative thioridazine was replaced by chlorprothixene in March 1967 The platelet counts then rose to > 40 000 and the leucocyte counts to > 4 000 The splenomegaly disappeared In September 1968 prednisolone was discontinued and in August 1969 chlorprothixene was replaced by haloperidol which shows no structural resemblance to the phenothiazines the platelet

TABLE II *Survey of 8 Cases of SLE Induced by Psychotropic Drugs Before and After Discontinuation of one or Several Drugs*

Patient	ANF	Class LE cell test	Hematological manifestations	ESR	Rheumatic manifestations	Additional findings	Psychotropic drugs given before occurrence of SLE symptoms (phenothiazines ital cs)	Changes after discontinuation of drug(s)	ESR	Class LE cell test	ANF
A ♂	+	Va	none	49	tendinitis		*perphenazine* orphenadrine	tendinitis disappeared	11	III V	(+)
B ♀	+	Va	none	7	arthritis metacarpophalangeal and interphalangeal joints		*chlorpromazine promethazine* amitriptyline	arthritis disappeared		IV	±
C ♀	+	V	none	55	polyarthritis		*chlorpromazine* [illegible] *perphenazine trifluopromazine* reserpine orphenadrine	arthritis abated before change of medication	4	III	±
D ♀	+	IV	none	42	periarticular swelling		*chlorpromazine levomepromazine* rescinnamine	arthropathic symptoms disappeared	22	neg	neg
E ♀	+	Va	leucocytopenia	15	none		chlordiazepoxide *perphenazine* amitriptyline	leucocyte count normalized	7	IV	+
F ♀	+	V	leucocytopenia	40	none	allergic skin reactions to ampicillin and chlorprothixene	*chlorpromazine* rescinnamine orphenadrine *thioridazine*	leucocyte count normalized	19	III	±
G ♀	+	IV	leuco and thrombocytopenia	51	none		*chlorpromazine promethazine* rescinnamine	leucocyte count normalized thrombocytopenia improved	10	III	±
H ♀	+	IV	splenomegaly hematomas leuco and thrombocytopenia	80	none	non specif syphilis tests circulat [illegible] of coagulant	*chlorpromazine* [illegible] *fluphenazine*	leucocyte count normalized thrombocytopenia improved splenomegaly hematom [illegible] disappeared	10	III	+ to ±

counts for the first time rose to > 100 000 The ANF test was still pos itive The LE cell test was class III At the Leiden hemostasis laboratory (Prof Dr F A Loeliger) a circulating anticoagulant was demonstrated in the patient s blood

In a gro p of 25 patients submitted to serological tests for ANF for *t rious reasons* (unexplained high ESR fever or many years of psychotropic medication) a dubiously positive ANF test and a class IV LE cell test were observed once

DISCUSSION

Table II presents the data on eight personally observed cases of psychiatric patients with a positive ANF test and a LE cell test of class Va or IV The data show that all patients but one had an increased ESR Four had hematological abnormalities (leucocytopenia < 3 000 thrombocytopenia < 100 000 and splenomegaly) Four showed rheumatic manifestations One patient had non specific syphilis tests and a circulating anticoagulant One patient responded to medication with allergic skin reactions

Since these patients were not suffering from rheumatoid arthritis hepatitis or discoid lupus erythematosus (in which positive LE cell tests also occur) they must be regarded as suffering from systemic lupus erythematosus (SLE) (4)

Since the patients showed clinical manifestations involving only one organ system (hematological or rheumatic) according to international agreement these syndromes must be recorded as possible cases of SLE Such authors as Kurland et al (7) classify all drug induced cases of SLE in this category

The eight patients described were seen in the course of five years among a mental hospital population of some 1 800 patients and with an annual turnover of some 500 cases this makes a total of some 4 300 patients This corresponds with an annual incidence (new cases per 100 000) of 36 The highest incidence of SLE so far observed anywhere (definite probable and possible cases jointly) was 16 (at Rochester seat of the Mayo Clinic (7))

The estimate of the general incidence in the Netherlands so far is 1 100 000 Consequently we maintain that the SLE morbidity in our two mental hospitals is much higher than the general incidence In our

TABLE III

List of Psychotropic Drugs Used

	Generic name	Trade name
Phenothiazines	chlorpromazine	Largactil
	levomepromazine	Nozinan
	perazine	Taxilan
	perphenazine	Trilafon
	perphenazine } amitriptyline }	Mutabon
	promethazine	Phenergan
	thioridazine	Melleril
	triflupromazine	Siquil
Benzodiazepines	chlordiazepoxide	Librium
Thioxanthenes	chlorprothixene	Taractan Truxal
	thiothixene	Navane
Rauwolfia alkaloids	rescinnamine	Moderil
	reserpine	*Serpasil*
Butyrophenones	haloperidol	Serenase
Antiparkinson drugs	diethazine	Diparcol
	orphenadrine	Disipal

opinion this must be considered as an effect of the long term medications *in our patients the majority of whom had been receiving psychotropic* drugs for several months to several years

An argument to support this contention is found in the improvement of the SLE syndromes following discontinuation of one or several psychotropic drugs in all cases Patients with rheumatic manifestations (A B C D) became asymptomatic an enlarged spleen (H) *became normal* leucocytopenia (E F G H) disappeared The increased ESR was normalized (A C E G H) or decreased (D F) Thrombocytopenia (G H) showed substantial improvement even though normal values were not yet attained The serological tests improved in all patients *In seven patients the positive ANF test became weakly positive (+) dubiously* positive ± or negative In all cases the LE cell test diminished by one or two classes or became negative The fact that not all manifestations (especially the serological) disappeared is consistent with experience gained elsewhere it can take up to nine years for all serological abnormalities *to disappear after discontinuation of the drug*

Improvement of the LE manifestations in our patients invariably followed *withdrawal of a phenothiazine derivative* In two cases an other psychotropic drug was discontinued at the same time as the phenothiazine derivative (reserpine in one and amitriptyline in the other case) in five cases, one or several other phenothiazine derivatives or other psychotropic drugs had been discontinued in the past without improvement or with less improvement than after discontinuation of the last phenothiazine derivative

The phenothiazine derivatives whose withdrawal coincided with the decisive improvement were chlorpromazine (2 cases) perphenazine (2 cases) promethazine (1 case) perazine (1 case) thioridazine (1 case) and levomepromazine (1 case)

Conclusive evidence of the LE inducing effect of phenothiazine de rivatives in our cases might be obtained be re administration However we do not feel justified in exposing our patients to such procedure

In summary we feel justified to state that phenothiazine derivatives can induce symptom poor LE syndromes which gradually improve after withdrawal of the offending drugs

Acknowledgement

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INTRA ARTICULAR INJECTION OF Y 90 RESIN COLLOID IN THE TREATMENT OF RHEUMATOID KNEE JOINT EFFUSIONS*

By

MARTTI OKA AHTI REKONEN AHTI RUOTSI and OLAVI SEPPALA

Summary A favorable effect was obtained in 20 out of 22 rheumatoid knee joints treated with 5—6 mCi of Y 90 Y 90 resin colloid produced a fall in synovial fluid leukocytes and enzyme activity Appreciable uptake of Y 90 in the regional lymph nodes occurred in some cases Bed rest clearly reduced the leakage of Y 90 The calculated radiation dose in the synovium at a depth of 1 mm exceeded 5 000 rad

Several reports on the use of radioactive agents for the treatment of chronic synovial effusions have been published (1 2 3 4, 9 15) The idea of using radioisotopes for this purpose came from earlier experience gained in the treatment of malignant pleural and peritoneal effusions with radioactive colloidal gold (Au 198) and yttrium (Y 90) The best analyzed data relating to the use of Au 198 in chronic synovial effusion were published by Virkkunen and co-workers (15) Among the 85 knee joints treated a favorable effect was obtained in 67 cases The period of observation varied from four months to two years in this series

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Preliminary report read at the XIII Scandinavian Congress for Rheumatology in Copenhagen June 7—10 1970

TABLE I

Comparison of the Radiophysical Properties of Y 90 and Au 198

	Au 198	Y 90
Beta energy (max.)	0.96 MeV	2.25 MeV
Gamma energy	0.41 MeV	—
Penetration range		
Maximum	4 mm	11 mm
Average	1 mm	4 mm
Half life	2.7 days	2.7 days

But there are serious disadvantages to intra articular Au 198 therapy In some cases radioactivity has been detected in the regional lymph nodes and liver in dangerous amounts The radiation dose for the regional lymph nodes exceeded 15 000 rad The radiation dose for the gonads was about the same as in an abdominal x ray These results (15) were confirmed by Grahame et al (4) but diffusion of radioactivity outside the treated joint was not reported by Makin and Robin (9) The difference is perhaps dependent on the size of the colloidal gold particles used (Virkkunen 200 Å Makin 700 Å) The larger colloid particles are thought to remain in the joint cavity better than the smaller ones

Delbarre and co workers (2 3) have made an extensive trial with radioactive isotopes in the treatment of persistent synovial effusion They observed a favorable effect in 87 per cent of the joints treated with Y 90 and a persistent cure in 56 per cent

As Y 90 is clearly superior to Au 198 in radiophysical characteristics (*Table I*) we have treated a series of rheumatoid knee joint effusions with this agent Our clinical results are reported in this paper In addition, the effect of Y 90 on some parameters of inflammation in the joint fluid has been followed The distribution of radioactivity in the organism has been measured and the radiation doses calculated

MATERIAL AND METHODS

The series treated with intra articular Y 90 injections consisted of 20 patients with rheumatoid arthritis A *total* of 22 Y 90 injections were given The majority of the patients had a long standing knee joint

TABLE II

Clinical Results of Y 90 Treatment in Rheumatoid Knee Joint Effusions

(F = female M = male D = decreased, A = absent, U = unchanged)

Case	Age and sex	Duration of effusion	Follow up months	X ray stage	Fluid amount	Pain	Change in joint circumference (cm)	Change in range of movement (degrees)
1	58F	>2 y	10	III	D	D	—4	+ 5
2	77F	2 y	12	II	A	D	—4	+25
3 a	19F	2 y	11	II	A	A	—3	+15
3 b	19F	2 y	10	II	A	A	—2	+15
4	28F	>2 y	6	II	U	U	0	+20
5	50F	>2 y	5	III	A	A	—9	+40
6	37F	6 m	5	I	D	A	—2	+50
7	35F	>2 y	6	II	A	D	0	+15
8	55F	>2 y	6	II	D	D	—2	0
9	45M	>2 y	6	II	D	A	—2	0
10	67F	2 y	7	II	A	A	0	0
11	47M	2 y	4	II	A	A	—2	+10
12	57F	2 y	4	II	A	A	0	+ 5
13 a	41M	6 m	3	I	A	A	—1	+ 5
13 b	41M	6 m	3	I	A	A	—1	— 5
14	56M	>2 y	2	III	D	D	—1	0
15	59F	8 m	2	I	A	D	—2	+ 5
16	63F	>2 y	3	II	A	A	—5	+25
17	31F	2 y	2	I	D	D	—2	+40
18	41F	>2 y	2	II	U	U	0	0
19	51M	8 m	1	I	A	D	—4	+20
20	60F	2 m	2	I	A	A	—5	0

effusion (1—17 years) which had resisted other forms of treatment including local hydrocortisone acetate in every case osmium tetroxide in six, Au 198 in one and surgical synovectomy in three But there were also five cases with knee joint effusion of shorter duration (2—8 months) More detailed data of the cases and of the results are shown in table II

The Y 90 was supplied to us from the Radiochemical Centre Amersham England It was incorporated in colloidal particles of Zeo Carb resin stabilized with glucose and gelatin particle size 300—500 Å

The specific activity was approximately 2 mCi per mg of stable yttrium The injected dose was 5—6 mCi in 19 cases and 3—4 mCi in three For the injection Y 90 was diluted with physiologic saline to a volume of 3—5 ml

The isotope was injected into the joint in a suspension containing 50 mg of hydrocortisone acetate and 5 ml of 2 per cent lidocaine Before the injection a synovial fluid sample of 10—15 ml was withdrawn We found that these adjuvants were of benefit in eliminating the joint pain which occurred when Y 90 was injected alone The injection was given in strictly aseptic conditions

To inhibit intra articular bleeding damage to the joint structures and leakage of Y 90 from the joint bed rest was ordered for three days after the injection During this immobilization passive joint movements were allowed This regime was not strictly adhered to in our first cases

The following studies were performed in each case before the treatment and at regular intervals during the observation period ESR blood picture Waaler Rose test Meulengracht SGOT SGPT urine sediment x ray of knee joint synovial fluid analysis including measurements of leukocytes granulocytes erythrocytes protein latex test muramidase activity (12) and acid phosphatase activity (7)

Local joint status was studied by observing the pain the range of movement the degree of periarticular swelling and hydrops and the knee circumference

Radioactivity was measured in blood and urine and on the injected and contralateral joint the inguinal lymph nodes liver heart and lungs The distribution of radioactivity in the injected joint the regional lymph nodes and the liver were visualized by gamma camera pictures (PhoGamma III Nuclear Chicago) The radiation doses in the synovial tissue and the regional lymph nodes were calculated The bremsstrahlung produced by the beta particles of Y 90 was measured as there was only negligible gamma radiation ($< 0.1\%$)

RESULTS

Clinical effect (Table II) Complete remission of rheumatoid synovitis was obtained in 10 of 22 injected knee joints Remission was partial in 10 cases and 2 failures were recorded The effect seemed

not to be clearly dependent on the duration of the disease or the x ray changes of the joint (14)

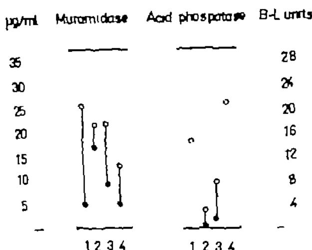
In both the failure cases treatment with osmium tetroxide had previously been tried without success On the other hand, there were synovectomized joints and osmic acid treated joints in which Y 90 injection proved very effective (Cases 1 3 7 17 18) The positive effect appeared gradually during two weeks Full remission was usually attained in 1—2 months All of the cases which responded favorably to Y 90 were still in remission at the end of the follow up period

The effect was demonstrated by disappearance or decrease of hydrops and joint pain increase in range of movement and decrease in joint circumference There were several cases in which the contralateral knee joint served as a control Local remission was achieved in 16 cases in spite of active arthritis in other joints The systemic rheumatoid activity was diminished in four cases at the end of the follow up period (Cases 6 15 16 19)

Case 3 is very illustrative and deserves special comment In this case both osmic acid treatment and surgical synovectomy had failed in the right knee and osmic acid treatment in the left Both knees were treated with Y 90 After 10 and 11 months of follow up there was no pain or effusion in the knees The patient could walk well, whereas before the Y 90 injections she had had to use crutches Arthritis was still active in several other joints muscular atrophy was marked, and the ESR was high In case 5 the knee effusion had persisted for many years and the x ray showed stage III changes After five months follow up there were no further signs of active synovitis in the injected joint The circumference of the joint was decreased by 9 cm and the range of movement increased by 40

No side-effects have been observed in the blood picture urine or liver function tests studied No fever reactions have been recorded Slight joint pain occurred only in a few cases during 1—2 days after injection of Y 90

Studies in joint fluid Compared to the pre treatment values a pronounced fall occurred in the number of leukocytes and granulocytes half an hour after the injection Synovial fluid samples drawn at later dates showed low leukocyte counts and a low granulocyte percentage when clinical remission was evident Slight bleeding into the joint fluid was observed in a few cases (up to 6 800 erythrocytes per cu mm) Synovial fluid protein and latex test showed no clear changes



F 1 Effect of intra articular injection of Y 90 on the activity of muramidase and acid phosphatase in the synovial fluid o = pre treatment activity • = activity half an hour after the injection.

The activity of the enzymes muramidase and acid phosphatase de creased strongly half an hour after Y 90 injection (Fig 1) In part this effect can be attributed to dilution of the synovial fluid In synovial fluid samples drawn at later dates the enzyme activities remained below the pre injection level

The inhibitory effect of Y 90 on muramidase and acid phosphatase activities could also be demonstrated in vitro 0 2 mCi of Y 90 in 0 1 ml of physiologic saline was added to 5 ml of 4 fresh synovial fluid samples and incubated at 37 C for 24 hours Muramidase activity dropped from 26—35 µg/ml to 5—13 µg/ml and acid phosphatase activity from 3 0—4 2 to 0 5—2 0 B—L units However nonradioactive yttrium resin colloid also had a very striking inhibitory effect on the enzyme activities in vitro In the same conditions hydrocortisone acetate and lidocaine had no effect

Distribution of radioactivity Fig 2 shows the retention of Y 90 in the treated knee joint of patient 6 In the figure there is also a line describing the radioactive decay of yttrium. The curve of retention goes below the decay line The difference of these curves represents the leakage of radioactivity from the knee cavity (in this case the leakage

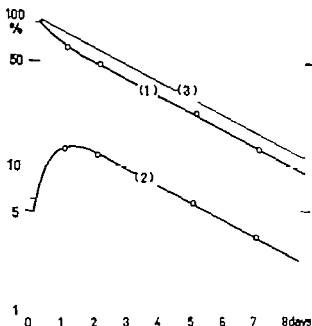


Fig 2 Retention of Y 90 in the knee joint (1) the radioactive decay of yttrium (3) and the leakage of radioactivity from the knee joint (difference of curves 3—1)

is 15 per cent of the injected dose) Patient 6 was one of the cases where immobilization of the treated limb was insufficient In the cases where bed rest after treatment lasted three days the retention curve showed less leakage from the joint (< 900 rad)

The uptake of Y 90 in the inguinal lymph nodes was measured in 19 patients The results are presented in table III Fig 3 shows some gamma pictures of different uptake patterns in the inguinal lymph nodes In the liver and lung region there was no detectable radioactivity

A typical curve representing the amount of Y 90 in the blood is shown in fig 4 The curve has its maximum a day after the injection The variation between the different patients was remarkable The maximal

TABLE III

Accumulation of Yttrium into the Inguinal Lymph Nodes and the Corresponding Radiation Doses

Number of patients	Y 90 in the lymph nodes	Absorbed doses in the lymph nodes
9	less than 1 per cent	less than 450 rad
3	1—2 per cent	450—900 rad
4	—5 per cent	900—2250 rad
3	5—10 per cent	2250—4500 rad

blood concentration varied between 0.01—0.5 per cent/liter. Equally large variation was observed in the amounts of yttrium excreted via the kidneys. The highest radioactivity in the urine was measured one day after the injection. The limits of variation were 0.1—2.0 per cent per day.

Dosimetry. The doses absorbed in the synovial tissue were calculated by the methods of Loevinger et al. (8). In these calculations the value 6 mCi was used as the injected activity. Fig. 5 shows the variation of the dose with the area of the synovium. The dose was calculated at a depth of 1 mm of tissue. The upper curve represents the situation when all the radioactivity is bound on the surface of the synovium (plane source) as shown by autoradiography by Webb et al. (16). In the case

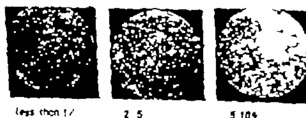


Fig. 5. Gamma pictures from the inguinal area showing different accumulation patterns of Y 90 in the lymph nodes.

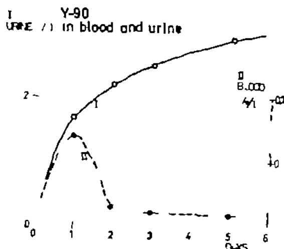


Fig 4 Yttrium activity in the blood (II) — dotted curve and scale — and cumulative excretion in the urine (I)

of the dotted curve and scale the yttrium is free in the synovial fluid (volume source) The actual situation is somewhere between the two curves obviously nearer the upper one From these curves we can conclude that the dose at a depth of 1 mm is more than 5 000 rad except in the very large cavity surfaces Fig 6 shows the variation of the absorbed dose with tissue depth

The absorbed dose in the inguinal lymph nodes is calculated from the formula (8) D = k f C E T where D = absorbed dose k = a constant (73 8 rad g/μCi MeV d) f = the fractional number of beta particles emitted per disintegration (1 beta/disintegration) E = the mean beta particle energy (0 93 MeV) C = the concentration of radioactivity in tissue (uptake in per cent x 6 000 μCi/20 g) T = half life of Y 90 (2 7 days) The calculation is based on an assumed delay of one day in the appearance of Y 90 in the lymph nodes corresponding to a correction factor of 0 77

Using the accumulation values obtained from measurements on the inguinal lymph nodes the absorbed doses can be calculated These are compiled in table III The doses were clearly smaller in the group of sufficiently immobilized patients all these doses were less than 900 rad The dose corresponding to the greatest accumulation was 4 500 rad

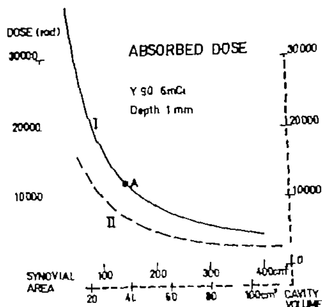


Fig 3 Absorbed dose of Y 90 as a function of synovial area and cavity volume
Curve I Yttrium bound on the synovial surface (plane source)
Curve II (dotted curve and scale) Yttrium free in the synovial fluid (volume source)

DISCUSSION

The clinical effect of intra articular Y 90 was beneficial in the great majority of patients treated Relief of pain and effusion and increase in joint mobility were long lasting and independent of the progression of the arthritis in other joints The effect also appeared in the inflammatory parameters of synovial fluid as a decrease of granulocytes acid phosphatase activity and muramidase activity It is evident that the initial acute effect of Y 90 on synovial fluid enzymes was a direct inhibitory effect The later changes in these joint fluid components followed the clinical improvement of inflammation

It was remarkable that there were cases in which all other forms of treatment including surgical synovectomy and local osmic acid had failed but Y 90 gave full remission In our view Y 90 can be used as an alternative to osmic acid and surgical synovectomy The advan

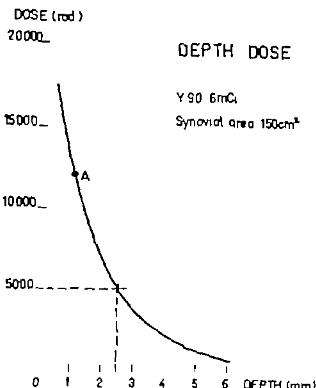


Fig 6 Absorbed dose of Y 90 as a function of tissue depth, corresponding to point A of curve I in fig 5

tages of Y 90 treatment compared to synovectomy are the ease of the procedure the prompt effect and the increase in joint mobility In our experience both Y 90 and osmic acid (5 6, 11) are very valuable agents in the treatment of persistent hydrops As yet it is impossible to say which of these two agents is the better

Compared with Au 198 Y 90 appears to be a more suitable radio isotope (Table I) It only emits beta rays with a high maximum energy and a maximum range in tissue of 11 mm The corresponding figures of Au 198 are much less effective The two isotopes have the same half life of 2 7 days In persistent knee effusions the synovium may reach a thickness of 1 cm Further disadvantages of Au 198 are the emission of significant gamma radiation and leakage from the injected joint into the regional lymph nodes liver and spleen in about one third of the treated cases (15)

Our studies on the distribution of Y 90 in the body showed appreciable leakage (10 %) of the isotope from the injected joint into the inguinal lymph nodes in a few of the cases This phenomenon could not be shown in the animal experiments performed by Webb et al (16) or in the studies performed in human RA by Prichard et al (13) A significant clinical finding was that this leakage could be reduced by bed rest for three days We have also consulted the manufacturer of Y 90 (10) about supplying us with a larger particle resin colloid But it appears that prevention of flocculation of the resin colloid presents technical problems which would be accentuated with larger particles

In this study the use of Y 90 was limited to knee joints only The agent can also be injected into some other big joints (elbow ankle shoulder) if the clinician can be certain of placing all the isotope in the joint cavity Otherwise radiation damage may occur The dose of Y 90 must also be adjusted according to the size of the joint to be treated For small finger joints Y 90 is less suitable because of its deep radiation range and the technical limitations of injection The optimal dose for the knee joints is 5—6 mCi according to the radiation dose calculations performed by us For children and adolescents intra articular injections of radioactive agents cannot be recommended

It is concluded that intra articular Y 90 is a very useful agent in the treatment of persistent knee joint effusion and preferable to radio active gold

Results of the uptake of Y 90 by synovial fluid cells and synovial membrane in rheumatoid knee joints will be reported in a subsequent paper

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Acknowledgement

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18 Dec 1970

SWEDISH SOCIETY OF RHEUMATOLOGY

Meeting in Stockholm 26th November 1970

1 TUBULAR KIDNEY DAMAGE ASSOCIATED WITH SLE

Borje Olhagen Arne Ljungqvist & Renee Norberg Department of Rheumatology and Department of Pathology Karolinska sjukhuset Stockholm

2 HEME SYNTHESIS ABNORMALITY IN RHEUMATOID ARTHRITIS

S V Johansson & Olle Strandberg Department of Clinical Chemistry and Department of Internal Medicine Karolinska sjukhuset Stockholm

In a study of heme precursors and enzymatic steps in heme synthesis patients with rheumatoid arthritis excreted increased amounts of porphobilinogen but normal amounts of delta aminolevulinic acid in urine This abnormality was in accordance with a high activity of delta aminolevulinic acid dehydratase in erythrocytes of these patients

3 RELIABILITY OF A QUANTITATIVE INFRARED THERMOGRAPHIC REGISTRATION OF KNEE JOINT ARTHRITIS

Bo Edstrom Department of Rheumatology Karolinska sjukhuset Stockholm

The present existing methods in rheumatology to quantify infrared skin emission are mentioned A survey is given of factors influencing on the equilibration of the skin to the environment during an examination

A new method is presented for quantitative evaluation of heat emission from knee joint arthritis using Bofors IR camera under appropriately standardized conditions The temperature is estimated for a reference point over the distal part of the foreleg compared with a black body by means of isotherm function The warmest points of the knees are measured in the same way from an oblique lateral view of 45 to the frontal plane The various temperature drifts during equilibration are estimated

on several occasions after undressing The absolute temperatures of the warmest points of the knees and their differences to the reference point are taken as quantitative measures of heat emission after proved equi brilation to the room

The reliability of the present method is shown by examining a patient with classical RA on an unchanged anti rheumatic medication During repeated examinations for three weeks there has also been a clinically confirmed constant activity of the disease

4 EXPERIENCES OF PENICILLAMINE TREATMENT IN RHEUMATOID ARTHRITIS

Per Olof Gedda Regionsjukhuset Örebro

5 TREATMENT OF RHEUMATOID ARTHRITIS WITH CYTO STATIC DRUGS A TRIAL WITH PODOPHYLLOTOXIN

Borje Olhagen Department of Rheumatology Karolinska sjukhu set Stockholm

6 SOME VIEWS ON PROLONGED TREATMENT OF URO ARTHRITIS (REITER S DISEASE) WITH ANTIBIOTICS

Lili Rosenthal Department of Rheumatology Karolinska sjukhuset Stockholm

A follow up study of patients with acute or chronic uro arthritis (Reiter s Disease) revealed a higher degree of functional capacity than similar earlier studies (Rosenthal et al Acta rheum Scand 1971) Out of 71 patients with this disease followed up for an average of 6 years 2 received disability pensions on account of iritis and 2 had been forced to change their occupation Out of 62 patients in whom there was no radiographic evidence of skeletal changes at the first examination 2 later developed radiographically confirmed changes in the sacro iliac joints and only 1 patient in both the latter joints and in the vertebrae

The treatment of chronic uro arthritis depends on the results of the urological examination Besides the conventional anti inflammatory treat ment with phenylbutazone or a cortisone preparation administered intra articularly alone or in combination we make every effort to overcome the urogenital infection with sulfa drugs using preferably sulfadimetoxin in doses of 0 5 g twice daily for one or two weeks and thereafter 0 5 g daily Alternatively we give broad spectrum antibiotics a trial using

generally tetracycline in doses of 1 g daily during the first week and thereafter a daily dose of 0 5 g With a view to long term prophylaxis of re infection chemotherapy or treatment with antibiotics is given for several months or years The line of thought prompting this method of treatment is the same as that underlying the use of penicillin to prevent infection by streptococci in rheumatic fever The problem associated with focal uro genital infection is that the discontinuance of chemotherapy or of the treatment with antibiotics may result in the recurrence of pros tatovesiculitis as well as of iritis and arthritis

A case is presented which illustrates this very clearly the patient had a recurrence on six occasions at intervals ranging from one week to five months, after the cessation of the treatment with tetracycline

7 POSTERIOR SUBCAPSULAR CATARACT ASSOCIATED WITH LOW DOSAGE CORTICOSTEROID THERAPY IN RHEUMA TOID ARTHRITIS

Ragnhild Gullberg Department of Rheumatology Karolinska sjuk huset Stockholm

Posterior subcapsular cataract (PSC) is a known complication of long term high dosage corticosteroid therapy But in the last four years accumulated cases of PSC have been observed in rheumatoid arthritis (RA) patients on long term *low dosage* corticosteroid therapy at the Department of Rheumatology Karolinska sjukhuset PSC was diagnosed in 8 RA patients Six of them had received paramethasone 1—3 mg daily one betamethasone 0 75 mg daily and one prednylidene 3 mg daily The last mentioned patient had been given also corticotropin The mean age at diagnosis of PSC was 53 (range 28—71) years In 4 of the patients PSC led to severe impairment of sight Because of the common use of chloroquine in RA at the clinic most RA patients are regularly checked at the Department of Ophthalmology Therefore there should be good chances of detecting early PSC Neither chloroquine nor any of the other pharmaceutical preparations given to the RA patients are known to cause PSC It should be noted that prednisolone is used as a standard drug for corticosteroid therapy at the clinic and that PSC was not detected in any of the RA patients treated with this drug It may therefore be suggested that not only the dose and the duration of treatment but also the type of corticosteroid preparation is of importance in the development of posterior subcapsular cataract

8 PARENTERAL IRON THERAPY OF ANEMIA IN RHEUMATOID ARTHRITIS

Olle Strandberg Department of Internal Medicine Karolinska sjukhuset Stockholm

A rather small proportion of patients with active rheumatoid arthritis have displayed signs of iron deficiency Twenty percent of 65 patients had no stainable marrow iron and a small group had increased rise in serum iron concentration in oral iron tolerance test Twenty patients were given Ferrigen (iron carbohydrate complex ASTRA) intravenously and 33 patients were given Jectofer (iron sorbitol complex ASTRA) intramuscularly One thousand mg was given in total to each patient The values for hemoglobin red blood cells and serum iron rose significantly during an observation period of 8 weeks in both groups The rise was slightly higher in the Ferrigen group possibly explained by the urine losses of Jectofer known to be about 30 per cent There were no complications recorded

Paulsen S & Iversen Th O Acta Rheum Scand 17 163—168 1971

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RHEUMATIC POLYMYALGIA

Long Term Treatment with Steroids

By

S Paulsen and Th O Iversen

Summary In 16 prednisone treated patients with the syndrome of poly myalgia rheumatica, the disease remained active during observation periods of 18—66 months The ESR was a reliable parameter of disease activity

In 1888 the Scottish physician Bruce (4) described a disease complex in five elderly men which he termed senile rheumatic gout The same picture was described in 1945 by the Danish physicians Meulengracht (10) and Holst & Johansen (8) In 1957 Barber (3) suggested the term rheumatic polymyalgia (r p) which has subsequently been the name most commonly used During the last fifteen years a great number of reports concerning this syndrome have appeared (2 5 6 7 9 11 12 13 14)

The duration of the disease is stated in literature to vary from one to four years Bagratuni (1) however found a mean duration of more than seven years in 50 patients

Since 1964 in the medical department of the Central Hospital at Holstebro we have like Wilske & Healy (14) used continuous steroid treatment

MATERIAL

The diagnosis has been based on a typical clinical picture and exclusion of other diseases The material will be found in table I Prednisone has

Presented at the XIIIth Scandinavian Congress for Rheumatology 7—10 June 1970

TABLE I

Pt no	Sex	Age at time of diagnosis	Observed no of months	Lowest dose following 3 months freedom from sympt	No of relap ses	Highest sed rate on relapse	Sed rate last control	Dosage at last control
1	m	65	66	5	2	58	7	2 5
2	f	51	63	10	1	21	20	10
3	f	60	63	5	2	55	12	5
4	f	71	60	7 5	2	85	18	5
5	f	65	42	5	1	66	10	7 5
6	f	67	42	7 5	1	24	15	7 5
7	f	75	42	5	1	90	10	5
8	f	65	42	7 5	2	41	21	5
9	f	68	40	7 5	2	—	8	5
10	f	69	36	5	2	102	25	5
11	f	69	25	10	1	50	19	10
12	f	66	36	5	0	—	28	5
13	f	66	32	5	0	—	28	7 5
14	m	69	24	5	0	—	20	5
15	f	67	24	5	0	—	16	5
16	f	73	18	5	0	—	7	2 5
Averages								
Total		66	41	6		—	16	6
Without relapse			27			—	20	5
With relapse			47			52	15	6

been given to all patients and the effect evaluated at the time of the first discharge The following criteria had to be fulfilled for satisfactory re mission 1 Striking subjective improvement 2 Normalization of the tem perature 3 Sedimentation rate of less than or equal to 20 mm/h

The patients have been under observation for periods from 18 to 66 months with an average of 41 months Observation was carried out dur ing short periods of admission to the department three or four times a year

RESULTS

Five of the 16 patients had no relapse during the period of observation No attempt was made to stop the treatment in these patients but the ob-

servation in their case was only 27 months The five patients concerned had no complaints at the last control in addition their sedimentation rate was 20 mm/h on an average and their dose of prednisone was 5 mg daily

The remaining 11 patients who have been followed for an average of 47 months have suffered a total of 17 relapses The term relapse is u ed when there was an obvious deterioration in the previous subjective symp toms and objective findings possibly with a subfebrile condition and an increase in the sedimentation rate followed by an outright improvement of both the subjective and the objective parameters after an increase in the steroid dose

The sedimentation rate was clearly increased to an average of 52 mm/h following a relapse On the whole the ESR appears to be the best objec tive parameter with which to evaluate the condition of the patient A sed imentation rate of more than 25 mm/h was rarely observed without sub jective symptoms of relapse Similarly clinical symptoms of relapse have not been observed except when the sedimentation rate was higher than 25 mm/h All the relapses observed occurred when attempts were made to reduce or stop the steroid treatment

The occurrence of relapses is distributed equally between the months of observation in particular there was no tendency for relapses to occur more frequently in the first year

The lowest dose of prednisone which could maintain the patient in a symptom free status was 5—10 mg on an average 6 mg per day whereas the average dose at the first discharge was 10 mg ranging from 5 to 20 mg daily

At the last control admission 2—4 months prior to this report 15 pa tients were well but one patient suffered from the sequels of a left sided femoral shaft fracture Four patients had developed an osteoporosis and one patient a slight diabetes

DISCUSSION

Since the disease remained active during the observation periods of 18—66 months the syndrome of polymyalgia rheumatica is not always a short lived disease Thus agrees with the observation of Bagratuni (1) The ESR was found to be a reliable objective parameter of disease activity and of response to steroid therapy

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Lindsay D J & al Acta Rheum Scand., 17 169—174, 1971

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SYNOVIAL IRRIGATION IN RHEUMATOID ARTHRITIS

By

D J LINDSAY E F J RING P F J COOREY and M I V JAYSON

Summary A double blind controlled trial was performed to compare synovial irrigation with simple aspiration of the rheumatoid knee By subjective and objective clinical criteria and by laboratory investigations of synovial fluid, it was shown that both groups of patients improved, but that joint irrigation afforded no additional benefit

A quarter of a century ago synovial irrigation (joint lavage) was being performed by some orthopedic surgeons prior to synovectomy of the rheumatoid knee (1) The interior of the joint and the state of the articular cartilage were inspected through a small suprapatellar pouch incision and fibrinous debris was removed by washing out with warm saline or dilute Eusol Painful knees were found to improve after this simple manoeuvre Hollander (2) Kodama (3) and Jayson and Dixon (4 5) have been impressed by the subjective improvement following synovial irrigation but these observations have been uncontrolled A double blind controlled trial was therefore performed to compare synovial irrigation *with simple aspiration of a rheumatoid knee*

METHODS

Twenty four patients with definite or classical rheumatoid arthritis (6) with painful knee effusions were randomly allocated into irrigation

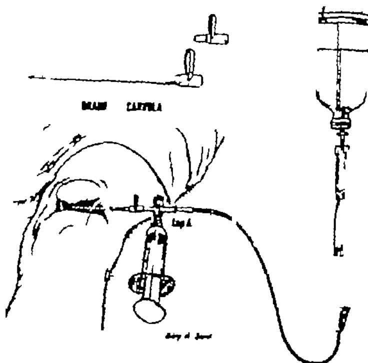


Fig 1 Apparatus used in irrigation and control patients

and control (aspiration) groups Practical procedures were performed by PFJC and clinical assessments by DJL, who was unaware of the treatment allocated All subjects were inpatients for at least the first three weeks during which time all forms of supportive hospital treatment were standardized

With full aseptic precautions a size 2 Braun cannula (internal diameter 1 45 mm) was introduced under local anesthesia into the joint from the lateral side (Fig 1) Any free synovial fluid was aspirated and saved for analysis A three way tap drip set and infusion bottle containing sterile 4 3 % dextrose 0 18 % sodium chloride were then attached to the cannula By means of a syringe attached to the side of the tap 50 ml volumes were withdrawn from the infusion bottle, and in the irrigation group injected into the joint reaspirated and discarded This was continued to a total volume of 500 ml In the control group the ten 50 ml volumes by passed the joint before being discarded

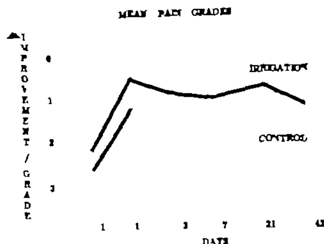


Fig 2 Mean pain grades of irrigation and control groups on each of the 6 clinical assessment days

Clinical Assessments

These were made on the day prior to treatment and after 1 3 7 21 and 42 days Pain was graded as nil (0) mild (1) moderate (2) and severe (3) Joint mobility was measured as the number of full knee flexions which the patient lying prone could perform in thirty seconds The range of knee movement was recorded by goniometer and the knee joint inflammation was measured by infra red emission from the skin over the patella as described by Cosh and Ring (7 8 9)

Laboratory Investigations

Synovial fluid was obtained on the day of treatment and by further aspiration at six weeks (42 days) when changes in viscosity (10) protein concentration Latex test, white cell counts and lactic dehydrogenase levels (11) were sought

Side Effects

The procedure though tedious was not unpleasant and no immediate or delayed adverse reactions or complications arose

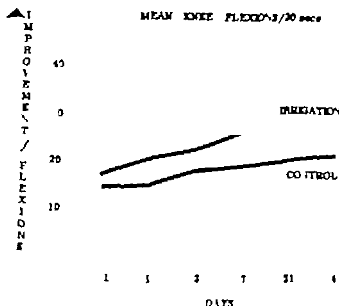


Fig 3 Mean number of knee flexions/30 secs of patients in irrigation and control groups at each of the 6 clinical assessment days

RESULTS

Ten irrigation and nine control subjects completed the trial While unrelated to the trial procedures the general medical management of a further five patients required them to withdraw from the investigation

Assessments of pain (Fig 2) joint mobility (Fig 3) and patellar skin temperature showed that both groups improved during the six week follow up period The changes were similar in both groups and no statistically significant differences emerged There was little significant change too in the mean range of joint movement following irrigation (Fig 4) Synovial fluid examination showed that viscosity increased in both groups at follow up There were no significant alterations in the Latex test protein content, white cell counts or lactic dehydrogenase levels

DISCUSSION

Uncontrolled observations in rheumatoid arthritis are renowned for their fallibility Many patients improve on admission to hospital irrespec

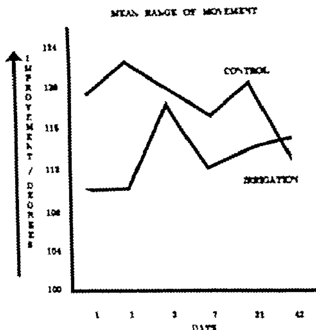


Fig 4 Mean range of knee movements as measured by goniometer in irrigation and control groups at each of the 6 clinical assessment days

tive of the treatment given This study confirms that simple aspiration of the rheumatoid knee is helpful but that the addition of joint irrigation provides no extra benefit Since the rheumatoid knee often contains large quantities of fibrinous debris enzymes and gamma globulin complexes logic might suggest that removal of this fluid is highly desirable (12) It might be that the cannulae used in the present study were of insufficient diameter to allow bulky debris to be washed out The improvements noted by Jayson and Dixon (4) followed arthroscopy where a 5 mm internal diameter cannula was used Andrews (13) prefers to use a hydrocoele cannula for knee joint irrigation Hollander (2) has on occassions used separate inlet and outlet cannulae to achieve a through flow of irrigating fluid and has found the technique of irrigation particularly useful in the treatment of popliteal cysts with highly viscous contents

Fibrinolytic agents have been used (2) to facilitate the procedure but in vitro studies (3) have shown that some 30—40 % of fibrin may remain undigested

Acknowledgement

We wish to thank Drs J A Cosh A St J Dixon and G D Kersley for allowing us to see their patients We are indebted to Dr R D Eastham Department of Pathology Frenchay Hospital for the measurements of synovial fluid viscosity MIVJ receives a Medical Research Council grant Fig 1 was kindly drawn by Mr G M James Medical Artist University of Bristol

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Rosenkranz M & al Acta Rheum Scand 17 175—186 1971

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THE REGENERABILITY OF THE SYNOVIAL MEMBRANE AFTER SUBTOTAL SYNOVECTOMY IN EXPERIMENTAL ALLERGIC ARTHRITIS

By

M Rosenkranz G Geiler and Ch Buhl

Summary It was possible to create a type of experimental arthritis which has great morphological similarity to human RA Its histological findings have remained unchanged over a period of one year In experimental allergic arthritis inflamed synovial membranes regenerate like normal synovial membranes, starting immediately after surgery and regeneration is complete on the 60th day Experimental arthritis is usually interrupted by removal of the inflamed synovial membrane

1 *Introduction*

The treatment of rheumatoid arthritis (RA) is now to a large extent influenced by the concept that RA is an immunological disease Treatment with immunosuppressive agents which aims at preventing the formation of autoantibodies that are important in the pathogenesis of RA (20) is unfortunately impeded considerably by the fact that the dosage required for adequate immunosuppression leads not only to damage of the immunocompetent cells but also of other strongly proliferating cells particularly the hemopoietic cells If one considers that the main site of immunological reactions in RA is in the synovial membrane of diseased joints it seems possible to eliminate the immunopathological reaction by removing the synovium For this reason synovectomy has firmly established itself in the past 5 to 10 years in the treatment of RA

The synovial membrane has an important arthromechanical function however and is important for the nutrition of the articular cartilage due to synovial fluid production. Therefore numerous problems arise regarding the late consequences of synovectomy for the joint. These are ultimately concentrated on the question whether or not after removal of the chronically inflamed synovial membrane an adequate regeneration product develops. But as *systematic investigation on humans is not* possible — the rare observations of synovial membrane findings in repeat synovectomy do not permit valid statements — the need arises to investigate experimental allergic arthritis.

2 *Experimental Allergic Arthritis*

Experimental allergic arthritis was produced in analogy to the method of Dumonde & Glynn (8) and Urbaszek, Rosenkranz & Schmidt (20).

We used rabbits of the same age and species and injected 1 ml of a mixture of Cohn's fraction I from human plasma and complete Freund's adjuvant (Difco) with a mixing ratio of 1:1 divided into 7—10 intracutaneous and subcutaneous injections. 1 ml of Cohn's fraction I was injected again six weeks later intra-articularly. 6 to 8 weeks after this (12 to 14 weeks after commencing the test) chronic arthritis was usually manifest. Morphological features were similar to those of human RA.

Before discussing the histological findings of the model let us first deal with the structure of the normal synovial membrane. We differentiate between a synovial intima and an adventitia. The cells of the synovial intima have been termed fibroblasts, epithelia, endothelia and mesothelia in alternation. His (11), Aschoff (2) and Kaufmann (15) assumed that what is called the intima originates from the mesoderm and has endothelial character. Other researchers thought that the intima develops by metaplasia of the connective tissue. Braun (5), Key (14, 15) and Vaubel (22) found that synovial cells in the tissue culture can be round, pleomorphous, *spindle-shaped and polygonal. They have* a tendency to develop synovial membrane and contain numerous *light* refracting granula which can be dyed by neutral red. In addition they produce mucin and fibrinolytic enzyme. Vaubel (22) calls them synovioblasts and suggests relations to the chondroblasts and osteoblasts. But he too admits a possible transformation of these *synovioblasts into* fibroblasts. According to the subsynovial tissue (synovial adventitia) *we differentiate* between three types of synovial membrane (14).

1 an areolar type
2 a fibrous type and
3 an adipose type

This differentiation is basically topographic Electron microscopy shows secretory and phagocytic (A and B) cells in the intima of the membrane (5) The cell layer generally consists of two to three layers In the adventitia beneath it one can recognise numerous blood and lymph vessels and rare mastocytes (7) macrophages and fibroblasts Key (15) and Fischer (10) saw numerous granula and small drops in cells of the adventitia which they thought to be mucin

After sensitisation and re sensitisation of the animals histology revealed considerable proliferation of the synovial intima with formation of mono- and polynuclear giant cells numerous papillae and pseudopapillae and increased vascularisation In some of the articular recesses there were glomerula like capillary loops In addition one can see superficial fibrinoid necroses and focal hyalinisation A large number of PAS and alcian blue positive granula are found in the cytoplasm of the intima cells Besides this there are scattered foam cells and a general abundance of acid and neutral mucopolysaccharides In the adjacent adventitia one can see many mostly perivascular lymphoblasts plasma cells and lymphocytes some of which form real lymph follicles and must be re garded as centers of antibody production Numerous granulocytes con taining PAS positive granula can be seen which correspond to what we call the rhagocytes well known in human RA The inflammation has spread focally to the peri articular tissue and led to extensive inflam matory changes One can detect changes similar to the muscle aggressive granuloma and a focal periarteritis

An effusion develops in the joint containing several cellular elements Their composition corresponds mainly to the acute phase of human RA We differentiate between the following cellular elements

1 granulocytes
2 histiocytes
3 lymphocytes
4 synovial cortical cells and degenerative forms of all types of cells

All morphological findings described are also found in human RA, so there is great similarity between allergic arthritis and RA

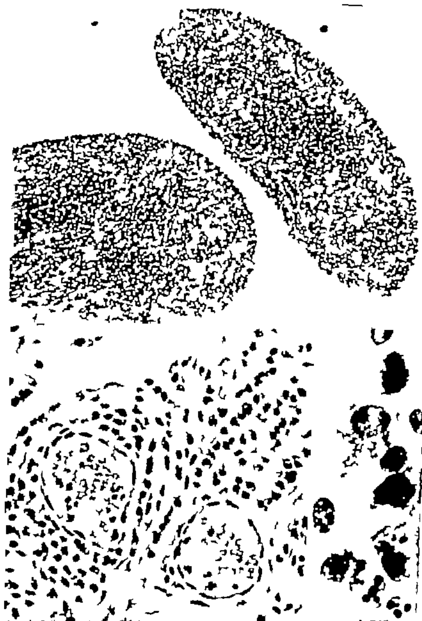


Fig 1 Experimental allergic arthritis with the formation of lymph follicles active hyperemia perivascular accumulation of plasma cells and several so called rhago cytes

) HE x 70 b) HE x 470 c) PAS x 840

Comparison of RA with experimental arthritis (EA)

	RA	EA
Acute, subacute, chronic and recurring synovitis	+++	+++
Villous hypertrophy	++	++
Lymph follicle formation	++	++
Cartilage destruction	++	(+)
Exudation	++	++
Periarthritis	++	+(+)
Ankylosis	+	(+)
Visceral involvement	++	+(+)

Below is our conception of the development of experimental arthritis

After application of the adjuvant/antigen mixture the RHS is stimulated by Freund's adjuvant and antigen is removed or phagocytosed by eosinophilic leucocytes and macrophages The antigen is distributed via the blood or lymph The antigen is phagocytosed and prepared by macrophages and acts as an antigen RNA-complex on the lymphocytes of the reticulohistocytotic system There it stimulates the lymphocytes and their metaplasia to lymphoblasts These must be regarded as antibody producing cells (19) The step from the cellular to the humoral phase of antibody production is now accomplished Thus we have antigens and antibodies and antigen/antibody complexes together in the blood So all of the three components reach the joint due to the good vascularization of the synovial membrane (4) and induce arthritis under the influence of complement by the liberation of lysosomal enzymes As the synovial membrane must be regarded as a part of the reticulohistocytotic system it participates intensively in the production of antibodies

3 *Investigation Material Operation Material and Material Processing*

We performed operations on a total of 36 rabbits We restricted ourselves to 10 normal animals and concentrated our work on 26 arthritic animals because data on the regenerability of the normal synovial membrane of rabbits are available since Key's (14) extensive and exact investigations The animals were killed between the 3rd and 202nd day after synovectomy i e up to 302 days after commencing the investigation at intervals of 3 6 10 and 12 days

About 100 days after beginning the investigation we operated upon the animals using intravenous Polamivet anesthesia and preventive

TABLE I

C urse of an Experiment with 11 Animals with Experimental Arthritis

Case	Commencement of experiment)	Reinsertion after days **)	Extent of the swelling of the joint 6—8 weeks after reinsertion left	right	Operation after commencement of experiment (days)	Operated joint	Killing after Operation (days)	Commencement of experiment (days)
335	12 9 68	58	+	+	97	right	5	100
332	12 9 68	58	+	++	96	right	6	102
337	12 9 68	58	++	+	98	left	14	112
333	12 9 68	58	++	+	97	left	18	115
3 7	12 9 68	51	++++	+	95	left	25	120
322	12 9 68	51	+	++	91	right	32	123
326	12 9 68	51	+++	+++	92	left	40	132
323	12 9 68	51	+	+	91	right	55	146
325	12 9 68	51	+++	+	92	left	100	192
329	12 9 68	51	++	+	95	left	125	220
330	12 9 68	51	++	+	96	Left	150	246

) Sensitisation with 1 ml of a mixture of Cohn I and complete Freund s adjuvant (1 1) divided into 10 intr and subcutaneous injections

) Injection of 1 ml of Cohn I per joint

administration of antibiotics A longitudinal incision was made in the skin medial to the patella with lateral opening of the joint Subtotal removal of the synovial membrane was possible in every case The capsule of the joint and the skin were subsequently sewn with a loop suture After this the knee joint was immobilised for a short time with a circular plaster slightly flexed because otherwise the animals would gnaw at the wound and make it impossible to heal without complication After removal of the plaster the animals immediately began to use the leg Normal motion was re gained within 14 days in all cases Table I shows a representative course of an experiment with 11 test animals

Histological examination was carried out with the material obtained by synovectomy and — after killing the animal — with specimens taken from the synovial membrane of the joint not operated upon The synovial membrane of the operated joint was investigated in three different places so as to check the regeneration of the membrane in all parts of the joint Investigations of cartilage and bone were not included here After this the tissue was fixed with 10 % normal formalin bedded in



Fig 2 3rd day after operation fibrin scurf with hemorrhages and few inflammation cells
Mallory x 210

paraffin cut and stained according to the following methods HE van Gieson PAS with control alcian blue fibrin stain after Mallory Gomori stain and Giemsa We assessed all sections according to a uniform method to obtain comparable results

4 *Findings and Discussion of Findings*

The joints were first assessed macroscopically after the operation This showed that in all cases the tendency to heal was surprisingly good and that a slight swelling of the joint occurred with exudation Motion was reduced only in the first days after operation so that the animals used the joint fully in the subsequent period After killing the joints were again examined macroscopically and it was found that in some cases focal fibrin deposits were still present 20 days after operation In others we found adhesions in the side recesses and brownish colouring which we explained as rests of hemorrhage in the regenerated memb ane In two cases we found free articular bodies in the articular space 150 days after the operation Cartilage and bone destruction could not be found macroscopically in any of the cases

— 8



Fig 3 18th day after operation initial regenerate with extensive increase of fibroblasts and beginning production of fibres
HE x 210

Regeneration of the normal synovial membrane starts as any wound healing process with the exudative phase i e with fibrin and leucocyte emigration from the hyperemic vessels of the capsule of the joint and the remaining rests of synovial membrane mainly in the recesses This regeneration takes a fixed course (14 15 16) which corresponds in the main to the regenerability of the inflamed synovial membrane in the experimental allergic arthritis that we produced

Regeneration of membranes changed by inflammation and removed at surgery also starts with extensive production of fibrin scurf into which erythrocytes macrophages few granulocytes and lymphocytes enter From the 3rd to 4th day the first adventitial and endothelial cells grow into the fibrin scurf from the damaged capsule of the joint The change over from the exudative to the proliferative phase is thus complete At this point the articular space is filled with an inflammatory exudate which contains a large number of cellular elements This fact and the presence of fibrinolytic enzymes are of paramount importance for preventing adhesions



Fig. 4 34th day after operation: areolar type of membrane regenerated, congested blood and lymph vessels: numerous fibroblasts with beginning formation of the synovial intima
HE x 210

The first fibroblasts may be seen on the 5th or 6th day which we believe to form the matrix for the regenerating membrane. Then fibre production begins: first resembling silver fibres and later looking like collagen fibres with constant increase of fibroblasts and ground substance. Whereas resorptive inflammation prevails in the first 10 days — regeneration becomes predominant in the subsequent period.

The acid and neutral mucopolysaccharide content of the ground substance increases continuously from the 10th to the 40th day only to decrease again up to the 60th day being associated with a general occurrence of fibres. Formation of the synovial intima begins between the 20th and 25th day and is complete between the 40th and 50th day.

In parallel to this development one can observe the production of glycoproteins in the intima cells which are a part of the synovia. Blood and lymph vessels are newly and completely formed at the same time with special precedence given to the areolar parts of the membrane. At first the lymph vessels are only slightly dilated. An almost complete regenerate is developed between the 50th and 60th day.



Fig 3 48th day after operation completely regenerated fibrous synovial membrane HE x 210

There is a clear difference between the regenerated tissue and the pre existing experimental allergic arthritis The typical histological changes of the pre existing arthritis can no longer be seen in any part of the regenerated membrane At surgery it was evidently possible not only to remove the inflamed synovial membrane and thus prevent the development of a pannus destroying the articular cartilage but also to interrupt the local production of antibodies In two cases we found a clear histological but only slight local relapse This corresponds approximately to the relapse rate in RA after synovectomy (5 to 10 %) The regenerated tissue differs from the normal synovial membrane only in its particularly firm adhesion to the capsule of the joint and a moderate proportion of fibres in the synovial adventitia

In conclusion we can say

1 It has been possible to create a type of experimental arthritis which has great morphological similarity to human RA Its histological findings have been unchanged over a period of 1 year

2 The normal synovial membrane regenerates completely which is in accordance with the information in the literature



Fig 6 Inflammation free regenerate 125 days after operation. HE x 210

3 Inflamed synovial membranes in experimental allergic arthritis have the same regenerability

4 Regeneration starts in both cases immediately after surgery and is complete on the 60th day

5 Regeneration starts from the damaged capsule of the joint and at the recesses from the remains of the synovial membrane

6 The fibroblasts play a decisive part in regeneration and form the matrix for the regenerate

7 Morphologically the regenerate may be regarded to be of full value It can provide nutrition for the cartilage of the joint

8 Experimental arthritis is usually interrupted by removal of the inflamed synovial membrane

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SCANNING ELECTRON MICROSCOPIC STUDIES

Fibrocartilage Degeneration in Rheumatoid Arthritis

By

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Summary The surface structure of the knee joint meniscus and the triangular fibrocartilage of the wrist in normal and RA joints were examined by scanning electron microscopy and histologically The surface of the normal meniscus showed a regular pattern of ridges composed of closely woven collagen fibre bundles In high power views the ridges were seen to be crossed by fine collagen fibrils The surface of the triangular fibrocartilage was smoother than that of the knee meniscus.

In RA desquamation of the collagen fibre bundles was revealed as an early change in more advanced cases also marked fraying of the bundles with inflammatory cells on the surface. These findings are discussed particularly in relation to the hypothesis that the disintegration of the fibrocartilage is caused by activated lysosomal enzymes

In rheumatoid arthritis the fibrocartilages of the knee distal radioulnar sternoclavicular and temporomandibular joints may undergo a rapid disintegration and finally completely disappear The destruction of the knee menisci in rheumatoid arthritis (RA) has been studied histologically and histochemically (1) The changes in the activity of fibrocartilagenolytic enzymes and in the viscosity of homogenates of rheumatoid menisci have also been examined (14) These authors suggest that

degeneration of the fibrocartilages may be caused in three ways 1 Fibrinoid necrosis of the concave surface caused by factors in the synovial fluid 2 Pannus like tissue originating from the inflamed synovial membrane causing superficial erosions 3 Granulation tissue invasion beneath the surface of the fibrocartilages causing softening fraying and finally total destruction

The scanning electron microscope (SEM) has been used to study the surface of rheumatoid joint cartilage synovial membrane and extensor tendons (7 8) No reports dealing with the SEM appearances of the fibrocartilages have been found in the literature

MATERIAL AND METHODS

Four samples of menisci were available from non rheumatoid knee joints one was obtained during a mid thigh amputation for tibial sarcoma and three were autopsy specimens One triangular fibrocartilage was available from the wrist joint of a young woman who had a sarcoma of the humerus The ages of the control patients varied from 18 to 63 years Only slight osteoarthritic changes were present in the radiographs of the older cases Seven knee menisci and one triangular fibrocartilage were excised during synovectomy in eight patients with definite or classical RA (11) The ages of these patients ranged from 5 to 50 years One discoid and two ruptured menisci were also examined All the specimens were prepared for both light microscopy and SEM for the former they were fixed by 10 per cent formalin and stained with Hematoxylin Eosin and Van Gieson s method for SEM the technique used has previously been described in detail by Fujita Tokunaga and Inoue (6)

RESULTS

Macroscopically the non rheumatoid control menisci were elastic and pearly white in colour Rheumatoid menisci were softened white or light yellow The convex borders of the rheumatoid menisci were invaded by villous synovium and ulceration was noted

Light microscopy A pattern of collagen fibre bundles and fibrocytes was seen in the menisci taken from the amputated extremity and from



Fig 1 Surface of the normal knee meniscus of a young adult x 500

the cadavers In the discoid and ruptured menisci similar findings were observed except in the injured areas where the collagen fibre bundles were frayed The rheumatoid menisci and triangular fibrocartilage contained small islets of proliferating fibroblasts In addition superficial fibrin deposits inflammatory cell foci and fibrinoid degeneration were observed These microscopic features were especially marked in the specimens showing the most advanced changes macroscopically A more thorough histochemical study of these alterations will be published later on



Fig 2 MRI changes in the surface of rheumatoid meniscus showing separation of the coll gen fibre bundles x 700

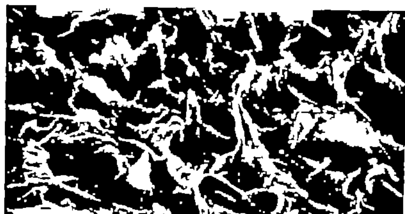


Fig 3 Marked degeneration of the rheumatoid meniscus is shown by fraying of the collagen fibre bundles and decrease in the amount ground matrix x 700

Scanning electron microscopy On the surface of the normal knee menisci there were regular ridges and grooves resembling intimately knitted woollen goods At a low magnification an interwoven network composed of ridges 8—9 μ in width was seen the ridges presumably correspond to the collagen fibre bundles (Fig 1) In higher magnifications the surface was crossed by fine fibres 0 1—0 4 μ in diameter corresponding to collagen fibrils The fibrocartilage from the normal wrist joint showed a more even surface composed of a network of collagen fibrils and ground matrix

The rheumatoid knee menisci with mild macroscopic changes showed here and there single collagen fibre bundles detached from the surface The ridges of collagen fibre bundles usually remained in their normal pattern and the ground matrix was not decreased (Fig 2)

The surface of the menisci of the rheumatoid knees with severe synovitis and joint destruction showed particularly marked fraying and splitting of the collagen fibre bundles and there were numerous inflammatory cells These changes may be seen in fig 3 where many of the collagen fibre bundles are seen to be standing up from the surface like coniferous lichen on rock A higher magnification revealed the collagen fibre bundles with their constituent fine collagen fibrils visible at the frayed ends inflammatory cells could be recognized among the bundles (Fig 4) Sometimes masses of inflammatory cells could be seen apparently forming a pannus like synovium invading the surface layer



Fig 4 A higher power view of fig 3 show the frayed bundles composed of collagen fibrils with inflammatory cells among them 1000

of the menisci (Fig 5) In the triangular fibrocartilage from the rheumatoid wrist joint there were masses of collagen fibre bundles partly desquamated from the surface and some spherical particles which were probably inflammatory cells (fig 6)

DISCUSSION

Intra articular discs and menisci have special importance in joint function particularly in the knee joint where also they are especially



Fig 5 A mass of inflammatory cells presumably corresponding to pannus like synovium x 550



Fig 6 Surface of a triangular fibrocartilage from a rheumatoid wrist joint with a mass of desquamated collagen fibre bundles and inflammatory cells attached to them x 1160

liable to degeneration and injury However there are few morphological studies of the fibrocartilaginous structures in healthy and diseased joints The histological structure of the normal menisci in the human knee joint was described by Bennett Davies and MacConaill (2) They showed that most of the collagen fibres run obliquely along the length of the menisci and are intimately woven into one another in the manner of basket work a few bundles run radially among those from the periphery Our findings using light microscopy and SEM are essentially similar The menisci are composed of a framework of interwoven fibre bundles with ground matrix between them This gives the typical elasticity of the normal meniscus The surface structure of the menisci is in many respects similar to that of articular cartilage (8) During the drying process of the specimen for SEM the meniscus shrinks considerably and thus it is possible that the ridges and grooves seen in SEM pictures of the normal meniscus are partly artefacts

Degenerative changes in the human knee menisci with advancing age have been shown by Bennett Waine and Bauer (3) Radial clefts and fraying were often together with thinning narrowing and calcium deposition In this SEM study on the other hand the surfaces of the menisci from the knee joints of aged cadavers showed a similar structure to those from young adults further SEM investigation into this point is clearly indicated

Our histological examinations of the rheumatoid menisci showed changes similar to those described in previous reports (1 14) The question arises as to the cause of the fibrocartilage degeneration It has been shown that enzymes of the joint fluid and those extracted from leucocytes and from rheumatoid granulation tissue have the capacity to break down the protein polysaccharide complex of cartilage (10 16) SEM reveals that the surfaces of rheumatoid articular cartilage and extensor tendons show many craters of various sizes and that there is marked fraying of the collagen fibre bundles on the surface of rheumatoid menisci At the stage of active inflammation numerous leucocytes are found in the craters The appearances suggested that the break down of the collagen fibre bundles may follow the disappearance of the ground matrix

It is of interest to speculate that some activated factors in the synovial fluid or the cells may affect the surface layer of the fibrocartilages Recently lysosomal enzymes released from inflammatory cells in the synovial membrane and the joint fluid have been suggested as a cause of the tissue damage and break down in RA (5 9 10 12 13 15 16) In vitro the break down of the ground matrix of articular cartilage has also been achieved by purified fractions (12) It has also been shown that the concentrations of several lysosomal enzymes are higher in degenerated parts of the rheumatoid menisci than in parts that are still healthy (14)

Our SEM findings are in keeping with the hypothesis that activated lysosomal enzymes damage the ground matrix of the fibrocartilages in rheumatoid joints In addition a collagenase which splits native collagen fibres has been detected in cultures of rheumatoid synovial membrane (4) It is reasonable to assume that the released enzymes first break down the ground matrix thus exposing the collagen fibre bundles to collagenases as well as to the constant wear and tear involved in the daily use of the joint

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EFFECT OF INTRAARTICULAR CORTICOSTEROID ADMINISTRATION ON ACID AND ALKALINE PHOSPHATASE ACTIVITY IN SYNOVIAL FLUID OF PATIENTS WITH RHEUMATOID ARTHRITIS

By

R K Lemperg G N M Beckman and L E A Beckman

Summary The effects of two steroid preparations (Hydrocortone and Celestona Bifas) on the acid and alkaline phosphatase levels in the synovial fluids were studied in patients with rheumatoid arthritis One knee joint was treated with steroid and the effects on the enzyme levels were followed in both the treated and the contralateral untreated joint Significant decrease of both acid and alkaline phosphatase was found in joints treated with Hydrocortone No significant effect was observed for Celestona Bifas The results suggest that the effects of Hydrocortone on acid and alkaline phosphatase were due to different mechanisms

INTRODUCTION

In rheumatoid arthritis increased levels of lysosomal enzymes have been found in the synovial membrane (2 8 15 17) and in the synovial fluid (2 3 9 19) The possible role of lysosomal enzymes in the pathogenesis of RA has been reviewed recently (6 7 14 16) The effect of glucocorticoids on lysosomes in vitro has been studied in several investigations Some investigators arrived at the conclusion that some steroids had a protective or stabilizing effect on the lysosomal membranes (18) while others could not find such an effect (4) In most of the in

vitro systems the stabilizing effect of steroids was studied by means of inhibition of labilization induced by different agents.

There is little information available on the effect of corticosteroids on the levels of lysosomal enzymes in the synovial fluid of patients with RA obtained under rigidly standardized conditions of treatment. Caygill and Pitkeathly (5) found a decrease of acid phosphatase and beta-acetylglucosaminase in three patients *after intraarticular administration* of hydrocortisone. The enzyme levels were measured before treatment and six to eight weeks thereafter. Jasini et al. (10) found somewhat higher enzyme values in a group of patients treated orally with corticosteroid compared to a group treated with salicylate. In the present communication we are reporting the effect of intraarticular administration of a hydrocortisone acetate and a betamethasone preparation on the acid and alkaline phosphatase levels *in the synovial fluids and serum* of patients with RA.

MATERIAL AND METHODS

All patients had a diagnosis of classical or definite RA with effusions in both knee joints. All were in-patients, the disease being in an active phase. All of them had received medication with salicylates and/or phenylbutazone or indomethacin for several months at the time of the study. This medication was continued unaltered. None of the patients had been treated intraarticularly with corticosteroids within six months before the start of the study. The consent of the patients was obtained that one knee joint would be treated with corticosteroid while both the treated and the untreated joints would be punctured in order to study the enzyme levels in the synovial fluids during the period of treatment.

Three groups of patients were studied.

A. Eight patients received a standard *dose of 0.5 ml Hydrocortone*© (Merck Sharp and Dohme) containing 25 mg hydrocortisone acetate per ml intraarticularly in one knee joint. Before the injection synovial fluid was aspirated from both knee joints and a blood sample was obtained. On days 3 and 10 the same procedure was repeated and the last samples of serum and synovial *fluids* were collected on day 17.

B. Eight patients received a standard dose of 0.5 ml Celestona© Bifas (*Schering Corp.*) *consisting* of 3 mg betamethasone disodium

TABLE I

Acid and Alkaline Phosphatase Activities in Serum and Synovial Fluids
[Patients in Group A before Treatment

Activities expressed as micromoles of alpha naphthol released per ml. fluid per hr (M ± S E)

	Acid phosphatase	Alkaline phosphatase	No examined
Serum	0 286±0 035	5 55±0 91	8
Whole synovial fluid			
Joint to be treated	4 12±1 08	5 30±1 24	8
Control joint	5 30±1 33	4 88±0 92	
Free activity in synovial fluid	18 %	85 %	8

phosphate and 3 mg betamethasone acetate per ml In other respects this group was treated in the same way as group A

C Sixteen patients received 0 5 ml Hydrocortone in one knee joint On day 7 synovial fluid was collected from the treated knee joint and another injection given On day 14 a second sample of synovial fluid was collected Only the treated joint was studied

In all three groups approximately 3—4 ml of synovial fluid were aspirated each time and no attempts were made to drain the joint

Immediately after aspiration the sample of synovial fluid was divided One part was frozen to —20 C (subsequently called whole fluid) One ml was centrifuged for 30 min at 4 000 rpm The supernatant was kept stored at —20 C The enzyme activity in this supernatant will be referred to as free activity The difference between the activity in the whole fluid and that in the supernatant will be referred to as bound activity

Acid phosphatase activity was measured at pH 5 0 (acetate buffer) and alkaline phosphatase at pH 10 8 (2 amino 2 methyl 1 propanol buffer) with alpha naphthyl phosphate as substrate (3) Starch gel electrophoresis was performed as described previously (3)

RESULTS

Table I shows the acid and alkaline phosphatase levels of serum and synovial fluids from patients in group A before treatment The alkaline

TABLE II

Effect of Intraarticular Cortisone Treatment on the Acid Phosphatase Level in Whole Synovial Fluids

Activity expressed as micromoles of alpha naphthol per ml fluid per hr (M ± S E)

	Initial activity day 0	Difference between day 0 and day 3	day 10	day 17
Hydrocortone				
Treated joint	4 12±1 08	—2 26±1 08	—2 30±0 25	—2 84±0 54**
Untreated joint	5 30±1 33	—1 26±0 64	—1 09±1 23	—0 60±0 9
Celestona Bifas				
Treated joint	2 74±0 92	—0 23±0 79	—0 21±0 47	—0 95±0 57
Untreated joint	3 11±0 81	—1 48±0 96	—0.20±1 18	—0 18±1 47

0 01>P>0 001
P<0 001

phosphatase levels in serum and whole synovial fluids were similar Most of the activity in the whole fluid was free activity (85 per cent) The acid phosphatase levels in whole fluids were in agreement with those found in previous studies of a large material of patients with RA (3) About 18 per cent was free activity The acid phosphatase level in serum was much lower than those of whole synovial fluid and the free activity

In group B the initial levels of acid and alkaline phosphatases in whole fluids were somewhat lower in other respects the findings were similar to those of group A In group C the initial acid phosphatase levels were somewhat lower than in group A and the alkaline phosphatase levels higher

Table II shows the effect of corticosteroid treatment on the acid phosphatase levels of the whole fluids in groups A and B

In the treatment with Hydrocortone (group A) a statistically significant decrease of the acid phosphatase was found in the treated joints on days 10 and 17 In the treatment with Celestona Bifas (group B) no significant effect was found In the Hydrocortone treated joints a significant decrease was found on days 10 and 17 also in the free activity The free activity on day 0 was 0 91 ± 0 25 and the differences between day 0 and days 3 10 17 were —0 54 ± 0 27 —0 73 ± 0 21 and —0 71 ± 0 20 respectively When Hydrocortone was administered

with 7 day intervals (group C) no significant effect was found on the acid phosphatase

Table III shows that treatment with Hydrocortone had a significant effect on the alkaline phosphatase level in the treated joint on days 10 and 17 and in the untreated joint on day 17

No effects of the treatment on the serum levels of acid and alkaline phosphatase were found

TABLE III

Effect of Intra-articular Corticosteroid Treatment on the Alkaline Phosphatase Level in Whole Synovial Fluids

Activity expressed as micromoles of alpha naphthol per ml fluid per hr (M ± S E)

	Initial activity day 0	Difference between day 0 and day 3	day 10	day 17
Hydrocortone				
Treated joint	3.30±1.24	−2.03±1.04	−3.54±1.26	−3.29±0.84**
Untreated joint	4.88±0.97	−0.53±0.65	−1.33±0.71	−1.42±0.58*
Celestone Bifas				
Treated joint	2.28±0.25	+0.25±0.65	−0.43±0.41	+0.16±0.38
Untreated joint	2.76±0.4	−0.51±0.56	−0.67±0.59	−0.94±0.53

* 0.05>P>0.01
** 0.01>P>0.001

By starch gel electrophoresis it was demonstrated that the synovial fluid had one isozyme component, which coincided in its electrophoretic mobility with the normally occurring (liver) alkaline phosphatase isozyme The two acid phosphatase isozymes typical of RA and other inflammatory joint disorders (2) were found in the synovial fluids of all patients When the acid phosphatase activity decreased due to treatment with Hydrocortone both acid phosphatase isozymes decreased apparently at the same rate

DISCUSSION

The results showed that intraarticular injections of Hydrocortone had an effect on the acid and alkaline phosphatase levels in the synovial

fluids of patients with RA The design of the investigation is crucial for the validity of this conclusion Patients with classical RA in an active phase are always subject to treatment of some kind Hence it is difficult to prove with certainty that a change in the enzyme level of the synovial fluid is due to the intraarticular administration of cortisone the change could be due to the effect of some other simultaneous treatment Since the present investigation allows a comparison between the treated and untreated joints, the influence of other factors can be separated from the effect of the local treatment with cortisone To our knowledge no other clinical investigation on the effect of local administration of cortisone has used untreated joints as controls

The evidence for an effect of Hydrocortone on the acid and alkaline phosphatase levels in the treated joint seems rather conclusive The possibility of a weak effect also on the untreated joint cannot be excluded, however There was a significant effect (on the 5 per cent level) for alkaline phosphatase on day 17 after Hydrocortone treatment Furthermore table II shows that in all cases (on days 3 10 and 17 for both preparations and both joints) there was a decrease of the acid phosphatase activity

The comparison between group A and group C indicates that the interval between the first two injections is important In group A the interval between the first two injections was three days, while in group C it was 7 days In the latter case no effect was found on the acid phosphatase level, but alkaline phosphatase showed a decrease

The comparison between the two kinds of steroid preparations revealed that Hydrocortone gave a statistically significant effect on both acid and alkaline phosphatase while Celestona Bifas showed no such effect The conditions of treatment were identical in the two groups The only difference between the groups was that group B (treated with Celestona Bifas) had a somewhat lower initial level of acid and alkaline phosphatase compared to group A (treated with Hydrocortone) There was however nothing to indicate that the decrease after treatment was correlated with the initial enzyme level

It seems likely that the mechanism of the cortisone effect is different for acid and alkaline phosphatase The data on the enzyme levels in serum and synovial fluid, the distribution on free and bound activity and the isozyme patterns suggest that the two enzymes have different origins Alkaline phosphatase in the synovial fluid occurred mostly as free activity and the electrophoretic mobility and serum levels coincided

with those of the major serum alkaline phosphatase isozyme. Its occurrence in the synovial fluid in RA may thus to a large extent be due to leakage through the synovial membrane though contributions from the synovial cells cannot be excluded. Acid phosphatase on the other hand occurred mostly as bound activity, the electrophoretic mobility of the isozymes did not coincide with those of the serum isozymes (3) and the enzyme level in synovial fluid was much higher than in serum. It is thus evident that acid phosphatase in the synovial fluid had a local origin mostly as fragments of cells from the synovial membrane and/or leukocytes. Furthermore there is evidence that the human acid alpha naphthyl phosphatases are lysosomal in origin (12).

In the present investigation cortisone may have had two effects: 1) to stabilize the lysosomes of the synovial cells, thereby decreasing the acid phosphatase level, 2) to increase the polymerization of the synovial hyaluronic acid (1), thereby decreasing the permeability of the synovial lining cells to serum proteins, i. a. serum alkaline phosphatase.

On inquiry about the subjective complaints most of the patients stated that they experienced an improvement. This improvement was similar in all three groups of patients, however, and apparently without any difference between treated and untreated joints.

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MUSCLE BLOOD FLOW IN RHEUMATOID ARTHRITIS

By

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Summary The MBF in the tibial muscle of RA patients was studied by a Xe 133 clearance method The MBF both at rest and after muscular ischemia was significantly reduced in RA The decrease in MBF was not clearly dependent on swelling of the neighbouring joints in the extremity studied The RA patients showed a greater increase in MBF after muscular ischemia than the controls

No correlation was observed between MBF at rest and the ESR Waaler Rose titer duration of the disease and age. In fresh hemiplegic cases there was no clear difference in MBF between the involved and contralateral extremity

The following conclusions were drawn 1 The reduced MBF in RA reflects the changes in the muscular microcirculation 2 The central nervous system plays no major role in the development of the diminished MBF in RA

Rheumatoid arthritis (RA) is a systemic disease in which manifestations of connective tissue disorder appear in different organs Wasting of muscles is a prominent feature of the disease This was noted as early as 1873 by Paget (9) Involvement of the voluntary musculature often occurs early in active RA In most instances the degree of muscular atrophy is proportionate to the severity of the articular disease Some

This study has been aided by grant from the Reumalisatto

times however the wasting may be out of proportion to the articular involvement and is found around joints with full range of movemen The muscular atrophy of RA is not attributed to disuse or immobiliza tion of joints

Several histologic studies have been performed on rheumatoid muscles Infiltrates of inflammatory cells have been commonly found (1) and nod ular lesions formed of focal accumulation of lymphocytes plasma cells and degenerated muscle fibers (12 13) In addition there are reports on clinical polyneuropathy in patients with RA (2) Electromyographic evidence of polymyositis was found by Steinberg and Parry (11) in 79 out of 93 patients with definite RA However these changes bore no constant relationship to the wasting and weakness of the muscles or the activity of the neighbouring joints

Haslock and his co workers (3) have recently described a series of 34 patients with RA with involvement of the neuromuscular system *Four patterns* were defined on the basis of the histology and clinical history These were 1 Connective tissue disease in the muscle including myositis chronic myopathy and polyarteritis 2 muscle cachexia 3 periph eral neuropathy 4 steroid myopathy

So far as we know there are no papers published on the muscle blood flow (MBF) in patients with RA In the present investigation the MBF of the lower extremities has been measured in a series of RA patients using a radioisotope clearance method developed by Kety (5) and Las sen (8)

MATERIAL AND METHODS

Our *series* comprised 36 patients with RA 17 males and 19 females The mean age of the patients was 45 4 ± 11 9 years (range 16—60) The duration of the disease varied from one month to 22 years (av 5 7) The control series comprised 19 cases — 6 males and 13 females 6 of the control cases were healthy persons and the remaining 13 were hospi tal patients without signs of rheumatic muscular or peripheral vascular disease The mean age in this group was 34 years (range 16 — 57) In addition MBF measurements were performed in two hemiplegic sub jects (age 48 and 55 years duration of hemiplegia 3 and 5 days)

The *method* was as follows The radioisotope xenon 133 (Xe 133) was dissolved in 0 1 ml of physiological saline The activity of this

volume varied from 500 to 100 μCi The half life of Xe 133 is 5 3 days and it sends gamma radiation of energy 80 keV The local radiation dose in this method is about 1 000 mrad and the whole body dose about 10 mrad

The disappearance of the isotope was measured with a conventional renography system consisting of a scintillation counter a rate meter and a chart recorder The skin crystal distance was 17 cm and the diameter of the field of vision 10 cm The range of the rate meter was 3 000 — 10 000 counts per second and the time constant 3 seconds

The *measuring procedure* Before the measurement the patient was kept in bed for 30 minutes The subject was studied in the supine position The isotope was injected slowly into the anterior tibial muscle and the collimated scintillation detector was directed to the point of injection

For the first 10 minutes the disappearance of Xe 133 was measured from the resting muscle Then the circulation of the leg was arrested by a femoral cuff inflated well above the systemic blood pressure During the five minutes of ischemia the distal muscles were exercised to the point of fatigue After the release of the cuff the clearance of the isotope reaches its maximum and can be seen as a deep fall in the curve

Calculation of the results The blood flow at rest and the maximal blood flow were calculated according to the formula

$$MBF = \lambda \times k$$

where λ (70 ml/100 g) is the equilibrium value of Xe 133 between tissue and blood k is calculated from the clearance curve by the equation

$$k = \frac{0\ 693}{T_{1/2}}$$

$T_{1/2}$ is determined from the initial slope of the measured curves after transferring them into semilogarithmic scale

RESULTS

In the RA patients the MBF at rest averaged 3 5 ml/min/100 g of tibial muscle with a standard deviation of 2 1 (Table I) The number of measurements was 66 In the control series the corresponding figures were 3 6 ± 4 0 in 55 measurements The maximal MBF in RA patients was 34 ± 13 ml/min/100 g in 24 measurements The corresponding

TABLE I

Results of Muscle Blood Flow (MBF) Studies in RA Patients and Control Cases Mean values and standard deviation

	MBF at rest (ml/min/100 g)	Maximal MBF (ml/min/100 g)
RA patients	3 5 ± 2 1 (66)	34 ± 13 (24)
Control cases	5 6 ± 4 0 (35)	44 ± 14 (23)
Statistical difference	$p < 0.001$	$p < 0.01$

( ) Number of measurements

figures in the control series were 44 ± 14 in 23 measurements There was a highly significant difference in the blood flow at rest between the RA patients and the control group ($p<0.001$) The difference in the maximal MBF was also significant ($p<0.01$)

The studied lower extremities of RA patients were divided into two groups The first group consisted of extremities with swelling in the knee or ankle joint or both The second group had no swelling in these joints In the first group the MBF at rest averaged 3 3 ± 2 1 ml/min/100 g and after circulatory arrest 32 ± 15 The corresponding values for the second group were 4 0 ± 1 9 and 37 ± 12

The muscle circulation was smaller in the group with swelling in the big joints of the lower extremities than in the other group but the difference was not statistically significant

No correlation was observed between the MBF at rest and the following parameters of RA 1 ESR 2 Waaler Rose titer 3 duration of the disease 4 age

To define the role of the central nervous system in the control of MBF measurements were performed in both legs of two hemiplegic patients No clear difference could be demonstrated in MBF at rest between the involved and contralateral extremity in these cases

DISCUSSION

Our results show that the MBF in patients suffering from RA is markedly decreased The decrease in MBF was not clearly dependent

on the swelling of the neighbouring joints in the extremity studied This may be an indication of the systemic character of RA

The changes observed in the blood flow of the resting muscle were more pronounced than those after arrested circulation The clearance method used for the measurement of MBF at rest indicates the capacity of the local microcirculation It has been shown that the vasculitis in RA affects not only medium sized and small arteries but also arterioles veins venules and capillaries The basic capillary vascular derangement in RA is characterized by excessive dilatation and leakage and could be the basis of the proliferative reaction and vascular obliteration in the connective tissue involved (6 7) Another factor which might in certain cases reduce MBF is local peripheral lymphatic blockade — a rare manifestation of RA (4)

In our studies on hemiplegic subjects we could not show a difference in MBF at rest between the hemiplegic and contralateral extremity This finding suggests that the central nervous system cannot be of major significance in the development of the diminished MBF in RA

The maximal MBF measurement is used in clinical routine to demonstrate occlusive processes in large blood vessels Minor changes cannot be disclosed by this method It has been assumed that the stimulus for the increased MBF after ischemia is the increased formation of lactic acid

As has been shown by Skrifvars and co workers (10) the larger arteries are not always intact in RA Premature arteriosclerosis was demonstrated in about 15 per cent of the cases studied compared with 3 per cent in the controls In the present study the increase in circulation after muscular ischemia was larger in cases with RA (x 10) than in the controls (x 8) This indicates that changes in the larger arteries had no significant effect on our results

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THE BIOSYNTHESIS OF COLLAGEN

By

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It is a long time now that rheumatologists have been interested in the biosynthesis of collagen the subject of the present paper It therefore seems natural to give an overall review of what we know at the present moment about this difficult problem Inevitably the biochemical aspect must dominate any such review

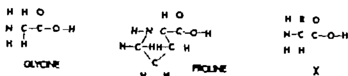
The Editor

Summary The author has reviewed the literature pertaining to the biosynthesis of collagen emphasizing those steps which are peculiar to the formation of this protein i e hydroxylation of lysine and proline, the formation of subunits and of intra and extra molecular bonds An account is given of the effects of vitamins and hormones on collagen synthesis. Possible alterations occurring in disease states such as hypothyreosis acromegaly Marfan s and Ehler Danlo s syndromes are discussed

Composition

Collagen is a glycoprotein which dissolved forms gelatine when heated This protein amounts to 25 % of all protein in humans and is present in all connective tissue There is always synthesis and degradation of collagen in the organism but in humans the turnover is rather

Partly rewritten after lecture given for the M D degree at University of Oslo May 1969



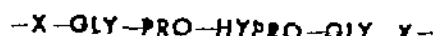


Fig 1 Composition of collagen Structural formulas for the two most important amino acids glycine and proline (line 1) The amino acids are bound together in a peptide chain (line 2) Each peptide chain is twisted (line 3) forming a helix around its long axis (line 4) The three peptide chains form together a triple helix (line 5) The tropocollagen molecules are building a collagen fibre by adhering to each other in a quarter staggered manner Ref 2 Reproduced with permission from J Gross Scientific American, 1960 240 121



Fig 2 Electron microscopic picture of a collagen fibre from human dermis Ref 2. Reproduced with permission from J Gross Scientific American 1960 240 121

slow ($t/2$ 1—2 years) (20) The synthesis may however be increased five times in a healing ulcer (34) Collagen has an unusual amino acid composition since 1/3 of the amino acids is made up of glycine Collagen is the only protein containing considerable amounts of proline and hydroxyproline (20 %) the incorporation of radio-labelled proline can therefore be used as a measure of the synthesis of collagen (for structural formulas of these amino acids see figs 1 and 5) Collagen also contains lysine and hydroxylysine which may bind the carbohydrate moiety (7 10)

The collagen molecule is made up of three peptide chains each being an alpha helix Each chain is twisted around the long axis with three amino acids per turn (Fig 1 line 5) These three alpha helices will also twist around each other forming a triple-chained helix a tropocollagen

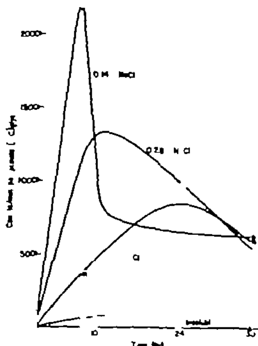


Fig 3 The specific activity of proline in fractions of soluble and insoluble collagen after injection of ^{14}C proline Ref 28 Reproduced with permission from Jackson, D S & Bently J P J Biophys biochem cytol. 1960 7 37

molecule (Fig 1 line 5) This molecule has a weight of about 300 000 dalton and a length of 2 800 Å Synthesized peptides of the structure poly (L prolyl glycyl L proline) will form a triple helix spontaneously in solution (41 52) Investigation of such model substances with x ray diffraction shows that this triple helix is very like the triple helix which is present in collagen in nature (52)

Forming a collagen fibre the single tropocollagen molecules adhere to each other side to-side and head to-tail all with their N terminal amino acids in the same direction The tropocollagen molecules are organized in a quarter staggered fashion i e there is a difference in the starting point of each chain of about 1/4 of their total length (Fig 1 below) The electron microscope picture of collagen fibres (Fig 2) gives the impression of periodicity most likely due to the binding of phospho-wolfram acid which — used as contrasting agent — will bind to specific polar amino acids (36) These polar amino acids are present at specific positions in the tropocollagen molecule

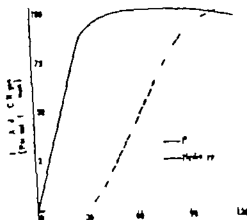


Fig 4 The formation of protein containing ${}^{14}C$ proline and ${}^{14}C$ hydroxyproline after incubation with ${}^{14}C$ proline Ref 51 Reproduced with permission from S Udenfriend Science vol 15 pp 1335—1340 fig copyright 1966 by the American Ass for the Ad ancement of Science

The N terminal end of the peptide chains does not participate in the formation of the triple helix This part of the chain contains neither glycine nor hydroxyproline while lysine has been identified as amino acid no 9 from the N terminal end (35) The N terminal end determines the immunological specificity and is degraded by proteases (9) This N terminal end is most likely the same as the telopeptides which should be responsible for the crossbanding of collagen

Solubility

Collagen is dissolved in 0 15 M NaCl more concentrated salt solution or citrate buffer The collagen which is dissolved in these different solvents has the same chemical composition but different physical properties After injection of radio labelled proline there is an early increase in the specific activity of proline in the fraction of collagen which is dissolved in 0 15 M NaCl (Fig 3) (28) This has been taken as an expression of the aging of collagen the newly synthesized collagen is the easiest to dissolve The young collagen (dissolved in 0 15 M NaCl) contains 90 % alpha helices and 10 % beta helices this ratio is inverse in the citrate soluble collagen It may be that this simple correlation between solubility and aging has to be changed since collagen from animals which had been labelled with proline six weeks before showed

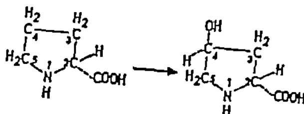


Fig 5 Hydroxylation of proline

a high specific activity in the insoluble collagen compared to collagen which was dissolved in salt solution (31)

Formation of Subunits

It has been suggested that the alpha helix consists of smaller units A great deal of work has been undertaken to study this question by the aid of ultracentrifuge technique These investigations have been heavily criticized by Speakman (48) and will therefore not be discussed here Some researchers have used the enzymes ribonuclease and collagenase The ribonuclease will degrade the m RNA which binds the ribosomes to polysomes The addition of ribonuclease to a collagen forming complex did not degrade it (18) The addition of collagenase gave rise to single ribosomes and made the collagen synthesis activity bind to polysomes of a smaller size These observations are compatible with the idea that the big polysomes are held together both by the m RNA and by the newly synthesized peptide chain It has been suggested that the big polysomes consist of pentamere or hexamere units which each are supposed to make a subunit of the alpha chain (18) The validity of the expression subunits of collagen (see later) is questionable however

Hydroxylation of Proline

In 1949 Stetton made an observation which for a long time was difficult to explain She found that ^{15}N radio labelled hydroxyproline when given to animals was not incorporated into collagen while some years earlier she had shown that radio labelled proline was a precursor to both proline and hydroxyproline (20) From these experiments was suggested that either prolyl sRNA a proline peptide or proline bound to protein was a substrate for hydroxylation





Fig 6 The intra cellular accumulation of collagen Autoradiographic picture of cell culture where the hydroxylation of collagen has been inhibited by cis fluoro proline (right) The radio labelled collagen accumulates within the cell (right) and is not secreted into the extra cellular substance as in the control (left) Ref 50 Reproduced with permission from Biochim Biophys Acta 1969 175 154 (fig 3 4)

Cells which are actively forming collagen have a high requirement of proline This need is covered by the conversion of glutamic acid into proline within the cell (27)

Peterkofsky and Udenfriend (51) were the first to show collagen synthesis in a cell free system By incubation with 14C proline there was a rapid formation of collagen containing radio labelled proline but a 30-minute delay before the appearance of collagen containing radio-labelled hydroxyproline Oxygen was not needed in the first period while it was needed in the second when hydroxyproline was formed Neither ribonuclease nor puromycin inhibited the formation of collagen containing hydroxyproline From these observations it was suggested that peptide bound proline or a protein with close relationship to collagen was a substrate for hydroxylation Such a collagen precursor (protocollagen) has later been isolated by Bekhor & Bavetta (4) The hydroxylation of proline is inhibited by a chelating agent alpha alpha dipyridyl Using this inhibitor and pulse labelling Bhatnagar & al (5) were able to show that both the peptide bound to ribosomes and the free peptides were hydroxylated at the same speed An intra cellular pool of protocollagen might be hydroxylated under certain conditions (46) The experimental situation will therefore determine whether the free or the ribosomal peptide is most important as a substrate for the hydroxylation (5 6)

In the hydroxylation of proline there is an absolute need for ascorbic acid ferrous iron alpha ketoglutarate and molecular oxygen (necessary for the formation of the hydroxyl group) Using a purified protocollagen hydroxylase Rhoads & Udenfriend (42) showed a stoechiometric relationship between the formation of hydroxyproline and the consumptio

of alpha ketoglutarate Collagen which is formed in the presence of alpha alpha dipyridyl (chelates Fe^{++}) has a low content of hydroxyproline and is very labile (12) The enzyme collagenase degraded this collagen five times as rapidly as normal collagen (26) This difference disappeared if the collagen was denatured in advance by heating (the heating process will make the triple helix open) This points to the importance of hydroxyproline for the stability of the triple helix in the collagen molecule Such collagen poor in hydroxyproline differs in other respects too it will not be secreted but accumulated within the cell (Fig 6) (29 50)

The hydroxylation of lysine is not effected by the protocollagen hydroxylase but by another enzyme The carbohydrates glucose and galactose are bound to the hydroxylysine in a two step reaction (7 10) The carbohydrate moiety must be present on the collagen for secretion of collagen from the cell (10 49 50)

Regulation of the Biosynthesis

It has been suggested that the biosynthesis of collagen is regulated by the hydroxylation of proline for instance through variation in the tissue levels of ascorbic acid alpha ketoglutarate or in the activity of the enzyme tropocollagen hydroxylase (20) It has not been possible to confirm these hypotheses by experimental evidence (19 20) When the biosynthesis of collagen was studied in cells which are replicating DNA synchronously the changes in the synthesis of collagen followed the variation in the synthesis of other proteins (14) This indicates that there is not a specific regulation of the biosynthesis of collagen through the transcription for this protein

Intra and Intermolecular Crosslinkings

In addition to the stabile bonds in young collagen there are some metastabile bonds which will change after the collagen has been laid down in the extra cellular substance The number of directly reacting aldehyde groups will be reduced with time (16) Many different observations on the aging of collagen and chemical basis can easily be explained from the formation of a delta 6–7-dehydrohydroksylysinoorleucine bond (Fig 7) $NaBH_4$ will stabilize this binding against acid hydrolysis The use of tritium labelled $NaBH_4$ gave rise to radio-labelled derivatives of lysine and hydroxylysine (2 3) When collagen was synthesized in the presence of radio-labelled lysine the specific activity per mole

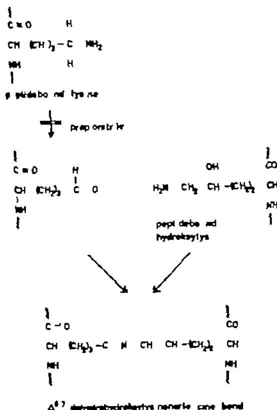


Fig 7 The formation of semilabile bond Peptide bound lysine (above left) is converted by an enzymic reaction into lpha amino-adipin gamma semialdehyde This reaction is inhibited by beta aminopropionitrile Alpha amino adipin gamma semialdehyde (left centre) condenses with peptide bound hydroxylysine forming Schiff base delta ⁸— dehydrohydroksylysinonorleucine bond

aldehyde group was twice as high as calculated per mole lysine (43) Lysine which is bound in a peptide linkage will be converted to alpha amino-adipin gamma semialdehyde (lysine aldehyde) by an enzyme lysyl oxydase which has recently been isolated from osseous tissue (38) Beta aminopropionitrile which inhibits this reaction gives rise to a collagen poor in aldehyde groups (15) Such collagen will be dissolved in salt solution to a higher extent than normal collagen (15 16)

It has been suggested that lysine aldehyde is not bound to the main peptide chain but to telopeptides separated from the main peptide chain by proteases These telopeptides will be responsible for cro

linking of the peptide chain Chemical analysis of the amino acids in a telopeptide did not show any hydroxylysine which would be present in the chemical linkage of delta 6–7 dehydrohydroksylysinonorleucine bond (30) From this observation it was suggested that the chemical bond goes from the teleopeptide in one chain to the body in another chain (2) These observations can be explained in another way The condensation reaction (which has been discussed above) will occur between lysine aldehyde and hydroxylysine but also between two molecules of lysine aldehyde (30 43 44) Lysine can be hydroxylated to a varying extent in different species It means that this chemical reaction in some species will mainly be a condensation reaction between two molecules of lysine aldehyde in other species between lysine aldehyde and hydroxylysine Lysine has been identified as amino acid no 9 from the N terminal end of the peptide chain but also close to the C terminal end (35) *This semilabile bond will therefore bind together the N terminal ends of two peptide chains or the N terminal of one chain to the C terminal end of another (intra and intermolecular bonds)*

Aldehyde groups will also contribute to more stable linkages in a collagen molecule In a disease state of lathyrism (after the addition of beta aminopropionitrile) there is a reduction both in the number of intra and intermolecular bonds (15) Beta aminopropionitrile inhibits the formation of aldehyde groups (Fig 7) (15 38) while pencillamin (beta beta dimethyl cystein) increases the number of such groups (15) Collagen which is taken from animals treated with beta aminopropionitrile shows an early aggregation when heated The close correlation between the content of aldehyde groups and the degree of aggregation in vitro of collagen both from animals treated with pencillamin and from hens with copper deficiency points to the importance of aldehyde groups for the crosslinking of collagen (11 15)

Collagen is degraded to fragments with a smaller molecular weight by addition of hydroxylamine (hydroxylamine will usually react with ester bonds) From these observations it was suggested that collagen was formed from subunits which were *held together by ester bonds These* hydroxylamine sensitive linkages are most likely not usual ester bonds (this would be rather unusual in a peptide chain) *they should be characterized rather as cyclic amides where the side chain in an aspartate is bound to the amide nitrogen in the following amino acid in the peptide chain* (8) *No specific enzyme has been shown to be responsible for the synthesis of this bond*

Deficiency of Vitamins C and D

It has been shown above that ascorbic acid is a cofactor in the hydroxylation of proline Deficiency of vitamin C will interfere with the biosynthesis of collagen also in other ways The fibroblasts will not develop into collagen forming cells and there is lipid deposition and increased cisterns within the cell (21) If the hydroxylation of proline was inhibited we would expect an accumulation of an intermediate rich in proline but poor in hydroxyproline No such intermediate is found It is more likely therefore, that ascorbic acid has an effect of different steps in the biosynthesis of collagen where the normal function of all these steps is necessary

In animals with vitamin D deficiency there is an increased rate of collagen synthesis (37) This collagen is more soluble in salt solution than normally Osteoblasts from animals deficient in vitamin D showed an increased glucolysis and also an increa ed formation of lactic acid

Hormonal Defects

Insulin will stimulate the synthesis of collagen in the presence of glucose (33) Growth hormone increases the formation of collagen (1) When growth hormone was given to patients with deficiency of this hormone there was an early increase in the secretion of hydroxyproline in the urine The high secretion of hydroxyproline and peptide bound hydroxyproline is in part derived from the protocollagen which is a precursor in the collagen synthesis but also from an increased degradation of collagen (39)

With increasing age in experimental animals there is a reduction in the biosynthesis of collagen a lower degree of hydroxylation and the collagen is less easily soluble All these changes can be reversed by estrogen (25)

Medically important is also the observation that terramycin inhibits growth calcium deposition and collagen formation in the fetus while there is no inhibition in the mother (23) It is likely that the increased synthesis rate in the fetus makes these processes more sensitive to inhibition than in the adult animal

Disease States with Changes in the Biosynthesis and Metabolism of Collagen

Patients with rheumatoid arthritis showed a low secretion of both proline and hydroxyproline in the urine (13) It is uncertain whether these

changes are primary or secondary to the disease In patients with Marfan s syndrome there is an increased turnover of collagen and the collagen is more easily soluble than usual (32) Aortic rupture has been observed in lathyrism which involves the formation of collagen Lathyrism was originally described as an acute intoxication after eating of sweet peas (Lathyrus odoratus) These peas contain beta aminopropionitrile which given to animals gives an abnormal growth of collagen tissue and dilatation of the aorta with rupture The beta aminopropionitrile has been very useful as an experimental tool for changing the solubility and cross linking of collagen The similarity between lathyrism in experimental animals and Marfan s syndrome does not imply that Marfan s syndrome can be explained by a similar inhibition defect which can be obtained by beta aminopropionitrile

Changes in the metabolism of collagen can also be used diagnostically and to follow an effect of treatment In hyperthyreosis there is a close correlation between protein bound iodine in plasma and the secretion of hydroxyproline in the urine (45) In acromegaly there is an increased secretion of hydroxyproline which will be reduced after successful treatment with x ray (39) It is rather difficult to evaluate the degree of disease in acromegaly both by clinical investigation and the usual biochemical tests It is possible therefore that the secretion of hydroxyproline or a specific peptide from collagen (47) should be used more often for the evaluation of this disease

Today we have accumulated considerable knowledge about the mechanisms in the biosynthesis of collagen But only after a more complete understanding of all different steps involved in the biosynthesis of this protein can we attempt a more rational approach to the study of patients with diseases such as Marfan s and Ehlers Danlos syndromes where primary defects in the biosynthesis of collagen may be present

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CULTIVATION OF A MYCOPLASMA FROM THE BONE MARROW IN SYSTEMIC LUPUS ERYTHEMATOSUS DISSEMINATUS

By

ELLI JANSSON* UNTO VAINIO and SIRKKA TUURI

Summary Using a modified cell free culture medium and a modern large viewfield microscopic equipment a mycoplasma was isolated from the bone marrow specimens of three patients with confirmed systemic lupus erythematosus disseminatus The three isolates metabolized arginine and did not ferment glucose or split urea A rabbit antiserum prepared against one isolate inhibited the growth of Mycoplasma arthritidis and strain 20 P from rheumatoid arthritis with a zone of 3 mm

It is fairly commonly held that systemic lupus erythematosus disseminatus (SLE) might be caused by an infectious agent probably a virus In fact Gyorkey and Kawano with their co-workers (1 2 3) found myxovirus like structures in biopsy specimens from patients with SLE Bartholomew (4) using cell culture methods isolated a mycoplasma from four out of six patients with SLE that he studied

This is a preliminary communication on the direct isolation on cell free media of a mycoplasma in three cases of confirmed SLE

MATERIAL AND METHODS

In summer 1970 bone marrow specimens from three patients with SLE were studied The microbiologic methods used are described in

detail elsewhere (5 6 7) In short the culture medium was that de scribed earlier (8) with the following modifications 1 Brain heart infusion broth was used instead of PPLO broth 2 To the broth medium egg yolk pasteurized at + 60 C for 50 min was added 0 1 ml to 10 ml of broth 0 5 ml of the crushed bone marrow specimen was inoculated into 5 ml of broth and incubated at + 37 C for 20 days Subcultures on mycoplasma agar plates were made after 10 and 20 days by inoculating 0 1 ml into the centre of small Petri dishes 5 cm in diameter which were incubated in an anaerobic milieu for 10 days Then they were examined using a Leitz Orthoplan microscope as described earlier (5 6 7)

RESULTS

The bone marrow specimens from three patients with confirmed SLE were studied On primary culture all gave growth of mycoplasma like colonies In one case (strain 338 M) several colonies were found in the other only one in the agar block cut off for microscopic examination In the subcultures tiny colonies appeared with a resemblance to those recovered in our laboratory from cases with rheumatoid arthritis (RA) (5 6 7) The figures 1—2 illustrate the microscopic appearance of strain 338 M The three isolates did not convert to bacteria when peni cillin and thallium acetate were omitted They required sterol for their growth They metabolized arginine and did not ferment glucose or split urea

A rabbit antiserum prepared against strain 338 M inhibited the growth of M arthritidis and isolate 20 P from RA with a zone of 3 mm M hominis M salivarium and M orale type 1 were not inhibited Strain 20 P was cultivated in 1964 at our laboratory from the synovial speci men of a woman with RA The present isolate 338 M from SLE shares the properties of those from RA (6 7) They seem to form a homo-geneous group sharing antigens with M arthritidis and a T strain myco-plasma from nongonococcal urethritis (9)

CASE REPORT

The patient from whom the strain 338 M was recovered was a wom an aged 32 In summer 1968 she fell ill with fever and pain in the



Figs 1 and 2 Isolate 338 M from the bone marrow in SLE 1st passage stained with Dienes stain in a 1 000 fold magnification

chest In hospital pleuropneumonia of the left lung was diagnosed The ESR was 124 Waaler Rose 500 Latex +++ direct Coombs test beta$_1$A ++ 1 40 nuclear antibodies (FA) total ≥ 1 280 IgG 1 1 280 IgM 1 320 LE cells were found six times Dg SLE Prednisone treatment was started and it had a beneficial effect

In March 1969 she complained of pain in her finger joints and shoulders On Jan 5 1970 she was admitted again because of pleuropneumonia of the right lung, which was treated with tetracycline On May 22 1970 she was readmitted because of pain in several joints The ESR was 124 Waaler Rose 500 Latex +++ direct Coombs test + anti IgG + nuclear antibodies (FA) total ≥ 1 1 280 IgG ≥ 1 1 280 IgM 1 320 Renal biopsy revealed changes compatible with chronic interstitial nephritis From the bone marrow specimen taken on May 28 a mycoplasma was isolated

DISCUSSION

This preliminary report shows that a mycoplasma strain from the bone marrow specimen of a patient with confirmed SLE has the same

properties as our isolates from RA Probably they should be included in a new human mycoplasma species sharing antigens both with M arthritidis and a T strain mycoplasma 71 T The latter was recovered in our laboratory from the urethral specimen of a male with nongonococcal urethritis (10)

During the present study in summer 1970 we did not handle M arthritidis reference strain No experimental studies were performed in the laboratory rats who may carry this mycoplasma species

However further investigations on a larger scale and in various qualified laboratories are still needed to clarify the possible role of mycoplasma in RA and SLE

Acknowledgement

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FURTHER STUDIES ON MYCOPLASMA IN RHEUMATOID ARTHRITIS

By

E JANSSON* P MAKISARA K VAINIO O SNELLMAN and SIRKKA TUURI

Summary Eight specimens of synovium and 19 of joint fluid from 27 patients with rheumatoid arthritis were studied on cell free media In most cases the clinical diagnosis was definite RA A mycoplasma was isolated in all cases Eight specimens showed tiny colonies in the primary culture eleven in the first passage seven in the second passage and one in the third passage The isolated strains required sterol for their growth and did not convert to bacteria when penicillin and thallium acetate were omitted Twelve specimens from patients with traumatic joint lesions studied concurrently by the same technique were negative for mycoplasma

Immune ascites prepared in mice against 19 isolates inhibited the growth of M arthritidis and strain 20-P By IHA technique 421 sera with a Waaler Rose titer of 128 or higher were studied, using as antigen the isolate 176-M

For many years investigators have been studying arthritis in animals caused by mycoplasma Sharp and Riggs (18) drew attention to the

This study was supported by grants from the Sigrid Jusélius Foundation the Finnish Medical Research Council and the University of Helsinki.

fact that Mycoplasma hyorhinis arthritis in swine very much resembles human rheumatoid arthritis Noteworthy features of this infection are the chronic nonsuppurative character of the inflammation the development of lymphoid follicles and the synovial fluid cytology

We began to study the possible role of mycoplasma in RA in 1963 Following on our earlier reports (9 10 11) we now present the last results

MATERIALS AND METHODS

Materials In winter 1967—1968 27 specimens from 27 patients with RA were studied In most cases the clinical diagnosis was definite RA (Table I) Eight specimens consisted of synovium and 19 of joint fluid Twenty one patients were under treatment at the Rheumatism Foundation Hospital at Heinola and six patients were seen at a Rheumatism Outpatient Clinic in Helsinki The synovial specimens were taken at Heinola in the morning put into sterile test tubes and sent by bus to Helsinki where they were inoculated immediately in the laboratory Simultaneously twelve specimens of synovium were studied taken from persons with traumatic joint lesions who were operated on at the Invalid Foundation Hospital in Helsinki

Isolation Technique The following medium was used Bacto brain heart infusion broth enriched with pooled heated human serum 20 per cent, yeast extract 2 5 per cent, glucose 1 per cent and 20 γ g per ml of D N A Egg yolk pasteurized at + 60 C for 50 min was added in amounts of 0 1 ml per 10 ml enriched medium into the broth This improvement of the broth medium was done as suggested by Marmion for antigen production (17) The agar medium was made smooth with 1 1 per cent agar In order to avoid bacterial contamination 500 units of penicillin per ml and thallium acetate to a final concentration of 1 2 000 were added The pH of the medium was adjusted to 7 8

The tissue specimens with some broth added were crushed in a mortar Then a loopful of this mixture or 0 5 ml of undiluted synovial fluid was inoculated into 10 ml of enriched brain heart infusion broth The broth cultures were incubated at + 37 C for 20 days and subcultures were made after 5 10 15 and 20 days by inoculating 0 1 ml on solid media Small Petri dishes five cm in diameter were used The cultures on solid media were incubated at + 37 C in an anaerobic milieu for 10

days In addition every specimen was inoculated on two blood agar plates for possible bacterial growth and incubated in an aerobic and anaerobic milieu for 4—5 days Blind passages were done three times by inoculating 0 5 ml of the broth culture into 10 ml of enriched broth medium and incubating again for 20 days

The agar plates were examined for growth under a low power microscope (x 100) The suspected growth was stained in situ with drops of 10 per cent Dienes stain as suggested by Hers (8) With this exception the method described by Madoff for identification of mycoplasma by the stained agar technique was followed (15) An agar block of about 1—1 5 sqcm was cut off mounted on a microscope slide with a cover glass and examined under 100 fold magnification with a Leitz Orthoplan microscope with an Achr 0 70/L 4 condensor Suspected colonies were examined with 540 fold or 1 000 fold magnification and an oil immersion lens The pictures were taken with a Leitz Orthomat camera

Biochemical Tests These were performed as described by Lemcke and Leach (14) except that brain heart infusion broth was used instead of PPLO broth Also the arginine containing medium was further enriched with cholesterol according to Taylor Robinson et al (19)

Preparation of Hyperimmune Sera The origin of the mycoplasma strains the antigen preparation and the immunization procedure have been described earlier (10)

Preparation of Immune Ascites in Mice In order to prepare immune ascites against the isolates these were grown in brain heart infusion broth enriched with 1 5 ml of pasteurized egg yolk per 350 ml of broth and incubated for 15—20 days A 200 fold concentrated antigen heated for 30 min at + 56 C was used for immunization CFW mice weighing 10—12 g were selected for this purpose four mice were used for every isolate Equal parts of the antigen and Freund's complete adjuvant were mixed and injected in 0 25 ml amounts intraperitoneally at 7—10—day intervals Six injections were given and on the last occasion Ehrlich ascites tumor was inoculated into every mouse as described by Wager and Rasänen (21) After about five to ten days ascites fluid developed, in some animals even before the tumor was inoculated The ascites fluid was harvested pooled for each isolate and checked for sterility It was stored at —20 C and used in growth inhibition studies

Growth Inhibition Test This was done according to Clyde (5)

—4



Fig 1 Strain 151 M 4th passa (100) All f gs show isolates from patients with RA

Indirect Hemagglutination (IHA) Technique Antigen was pre pared of strain 176 M as for rabbit immunization except that it was un heated and sonicated for 2 min in a model MSE 100 Watt ultrasonic disintegrator The technique reported earlier by other workers for my coplasma antibody studies was used with fresh tannic acid treated erythro cytes (6 20) Bovine albumin (from Sigma Chemical Co) was added in the ratio 1 25 to the dilutant

RESULTS

Isolation Studies A mycoplasma was isolated from everyone of the 27 specimens studied Twelve specimens studied simultaneously by the same technique from traumatic joint lesions were negative for myco plasma There was no bacterial growth on blood agar from the original samples Eight specimens showed tiny colonies resembling mycoplasma in the primary culture eleven in the first passage seven in the second passage and one in the third passage

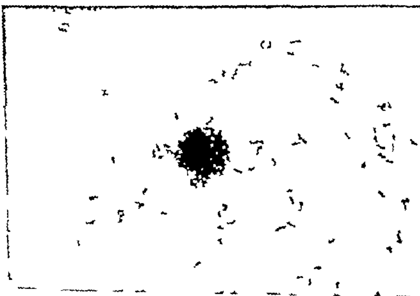


Fig 2 Strain 138 M th passage (x 540)



Fig 3 Strain 138 M 9th passage (x 1 000)



Fig 4 Strain 152 M 7th passage (x 1 000)

In the primary cultures and in the first passages as few as one to four tiny colonies were observed as a rule in the agar block cut off for examination with the large viewfield Orthoplan microscope In later passages the number of the colonies increased and many colonies could be seen in the same field as can be seen in fig 1 All the isolates required sterol for their growth They were inhibited by tetracycline and did not convert to bacteria when penicillin and thallium acetate were omitted

None of the isolates showed large typical fried egg forms with a dark centre and a light periphery Usually the colonies were very tiny about 1/10 to 1/100 of the large-colony mycoplasma However with Dienes stain and an oil immersion lens the fragile granular structure could be seen clearly as illustrated in figures 2—4

Table I shows the clinical diagnosis of the patients results of Waaler Rose and Latex tests, and also if treatment with steroids had been given

Biochemical Studies The isolates did not ferment glucose or split urea but they were arginine positive

Growth Inhibition Studies Because the isolates did not form colonies visible to the naked eye immune ascites were prepared in mice against

TABLE I

S m Clinical Data | the Patients

Number of patients	Diagnosis	Waaler Rose and/or Latex positive	Treatment with steroids
20	Definite RA	16	5
1	J enile RA	—	—
4	Probable RA	—	—

Waal r Rose positive with titer ≧ 128
The hospital record of two patients wer not av ilable

nineteen strains These were tested against known mycoplasma species M hominis M salivarium M orale type 1 M fermentans M arthritidis M pulmonis and M gallinarum They were also examined against a strain (20 P) which was isolated by us in 1964 from synovium of a patient with RA This strain seems to be related to M arthritidis (10) All nineteen immune ascites inhibited the growth of this strain and M arthritidis with an inhibition zone of 3—5 mm They did not inhibit the other mycoplasma mentioned

Antibody Studies By IHA technique 421 sera with a Waaler Rose titer of 128 or higher were studied using as antigen the isolate 176 M 127 sera (30 per cent) showed titers ≧ 8 In 81 cases (19 per cent) the titers were ≧ 16 fifteen cases revealed a titer of 16 sixteen 32 thirteen 64 nineteen 128 four 256 seven 512 six 1 024 and one 16 384 Table II shows that there seems to be antigenic variation between different isolates

DISCUSSION

In the 1960s several workers have studied the possible role of mycoplasma as a trigger mechanism in the pathogenesis of RA (1 2 5 15) Fahlberg et al (7) obtained mycoplasma from synovial tissues or fluids of 22 out of 24 patients with RA Williams (22) found a mycoplasma serologically related to M fermentans in 40 per cent of 90 synovial fluids from cases of active RA Recently Marcolongo et al (16) recovered mycoplasma from synovia of 43 out of 58 patients studied Our

TABLE II

Mycoplasma Antibody Titers in Some Waaler Rose Positive Sera Examined with Four Antigens

Specimen Number	Antibody Titers			
	5—M	56—M	176—M	135—M
312—R	64	<16	512	<16
4570—R	512	128	256	<16
4666—R	64	256	64	<16
4745—R	≧1 024	32 768	16 384	4 096
615—R	16	256	128	<16
125—R	16	<16	56	<16
518—R	2 048	256	128	8 19
133—R	32	<16	256	<16
16—R	2 048	128	256	1 024

5 M = isolate from juvenile RA 56 M and 176 M = isolates from definite RA
133 M = isolate from the bone marrow specimen of a boy with acute leukemia

isolation incidence very much resembles those of Fahlberg et al and Marcolongo et al

The need for a very good culture medium and first class microscopic equipment for the isolation of fastidious mycoplasma cannot be over emphasized These problems will be discussed separately (12) Suffice it to recall here that after a minor modification in the usual PPLO medium Hayflick succeeded in growing Eaton agent on cell free media In our opinion the addition of fresh pasteurized egg yolk to mycoplasma broth medium was an important improvement This could of course be criticized by asking whether it might introduce an avian mycoplasma into the medium If it does it would probably be the glucose fermenting M gallisepticum colonies of which are much larger than those of our isolates The results of growth inhibition tests show that not another avian mycoplasma M gallinarum was present In addition the cultures of egg yolk from 24 hens eggs were negative for mycoplasma Because mycoplasmas are heat sensitive the enrichment of the broth culture medium with pasteurized egg yolk probably is safe

During the present study no other known human mycoplasma than M pneumoniae were handled in our laboratory Our isolates from RA seem to make a homogeneous group sharing antigens with M arthritidis However studies in other laboratories are still needed to clarify the possible role of mycoplasma in RA

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AN ACUTE IMMUNE RESPONSE TO INTRA ARTICULAR INJECTION OF OSMIUM TETROXIDE

By

Y Collan C Servo and I Winblad

Summary A systemic reaction to intra articular injection of osmium tetroxide is described The patient, a 49 year-old woman, with RA and a history of drug allergy had been treated with an osmium tetroxide injection in her right knee four years before osmic acid was injected into her left knee After the injection she got high temperature, chills and erythema After the acute phase kidney and liver damage could be recorded

Intra articular osmic acid injections for the treatment of RA are not recommended for patients with a history of drug allergy

INTRODUCTION

Intra articular injections of osmium tetroxide for the therapy of rheumatoid arthritis were proposed by v Reis and Swensson (12) about 20 years ago Since then this treatment has been used in selected cases to avoid operative synovectomy and to prepare patients for operation (2 4 5 6) Although osmium tetroxide is an effective fixative (11) an intra articular injection causes only a local inflammatory reaction which subsides in a few days Besides the initial rise in temperature no systemic reactions have been reported even after successive intra

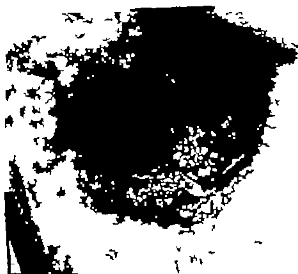


Fig 1 Ulcer at the right knee earlier osmic acid treated after osmic acid injection into the left knee joint cavity

articular injections In this article we present a complication of this kind of therapy which did not seem to be due to the acute toxicity of osmium but rather was caused by sensitization

CASE REPORT

The patient was a woman of 49 She had a seven year history of definite RA and had suffered from several respiratory infections and allergic dermatitis reactions She was treated with gold (total dose of 10 g sodium aurothiomalate) in 1964 but the treatment had to be interrupted because of dermatitis and again in 1966 (1 g) Since then she has been kept on a small dose of prednisolone and chloroquine

Osmium tetroxide 100 mg was injected into the right knee in 1966 with good therapeutic results A cyst later appeared on the back of this knee with a fistula which had healed at the time of her second osmium tetroxide injection in the opposite knee In January 1970 100 mg osmium tetroxide with lidocaine 50 mg and prednisolone 40 mg were injected into the left knee Three hours later chills and high fever with mild erythema on the body developed Both knees became acutely

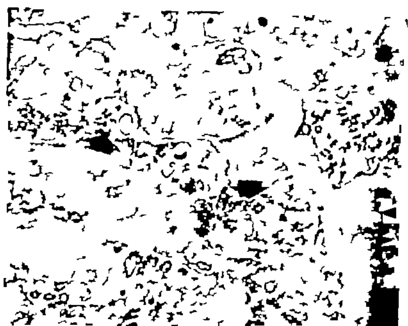


Fig 2 Light microscopic findings of the liver 2 weeks after the injection Parenchymal liver cells appear normal but the number of Kupffer cells is increased and there are numerous cytosomal granules in their cytoplasm (arrow) x 400

swollen red and tender The reaction subsided in three days but on the third day the serum creatinine was found to have risen to 130 μmol/l (1 5 mg %) The urine showed a weakly positive protein reaction with some granular casts in the sediment No change in the volume of urine occurred Concurrently signs of progressive liver damage appeared GOT was elevated from 67 IU on the third day to 190 IU on the seventh day (normal < 20 IU) GPT correspondingly from 35 to 222 IU (normal < 30 IU) and alkaline phosphatase from 4 8 to 20 4 BL units The signs of kidney and liver damage disappeared within a week

The scar from the fistula in the right dorsal popliteal fatty pad and the surrounding tissue became necrotic within the first 24 hours after the osmium tetroxide injection A deep ulcer 3 cm x 4 cm (Fig 1) developed but did not penetrate into the intra articular space The ulcer granulated rapidly and a biopsy specimen showed granulation tissue with a few foreign body giant cells No foreign material was detected in the specimen

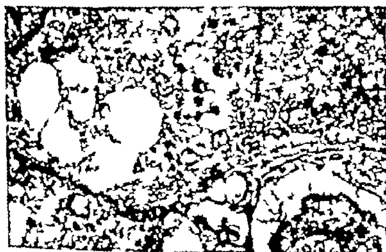


Fig 3 Electron micrograph of three liver cells Sinusoid at the right corner Large vesicles are seen in the cell at the left N = nucleus S = sinusoid x 8 300

Liver biopsy was carried out two weeks after the injection PAS staining of paraffin sections showed no abnormality Epon embedded sections stained by methylene blue revealed local accumulations of Kupffer cells with numerous lysosomal granules (Fig 2) Some vesicular vacuoles were found in liver cells Electron microscopy showed liver cells with large vesicles (Fig 3) No increase in liver parenchymal cell lysosomes was found

Kidney biopsy was carried out 3 weeks after the osmium tetroxide injection The light microscope specimen showed changes of chronic interstitial nephritis with edema and slight fibrosis Tubuli appeared normal Electron microscopy of the glomeruli showed enlarged mesangial areas with thickening of the basement membrane No deposits were seen connected with the basement membrane (Fig 4)

In unstained sections of the liver and kidney no evidence of osmium tetroxide deposition was found Considering the small amount of intra articularly injected material this finding was not surprising

DISCUSSION

Osmium tetroxide has been used intra articularly in the treatment of RA for about 20 years and the kind of complication described has



Fig. 4. Electron micrograph of a glomerulus. Note the thickened basement membrane in the mesangial areas. At C a capillary loop with thickened endothelium and fused epithelial cell foot processes on the basement membrane. × 4 100

not been previously reported Some osmium tetroxide injected into the articular space is fixed in the synovium and some obviously leaves the cavity by the way of the lymphatics which traverse the fatty tissue around the knee Much of the osmium is fixed in this fatty tissue because of the strong lipophilic nature of the substance (9) Osmium can be detected in fatty tissue for years after the injection (8) The reaction to the second injection was obviously an immunological phenomenon osmium tetroxide probably participating as the hapten This substance has a strong affinity for several tissue components especially lipids but also proteins (11) Quite obviously osmium tetroxide lipid or osmium tetroxide protein complexes will be liberated in small amounts into the circulation soon after intra articular injection The patient s history with former drug reactions suggests an allergic constitution (7) which would explain this unusual complication The local reaction in the contralateral knee can be interpreted as due to local sensitisation to osmium tetroxide in this area

The findings in liver and kidney should be interpreted with care because the acute phase had subsided at the time of biopsy and because histological changes in liver (14) and kidney (10) are known to occur in RA However liver biopsy revealed increased amount of Kupffer cells which must be considered an unspecific change — possibly due to parenchymal cell destruction which was also reflected in the abnormal transaminase values The vacuoles found in liver cells were similar to vacuoles seen in connection of anoxic (1) injury or in chronic congestion of the liver (3) Sabesin (13) caused an experimental allergic hepatic necrosis with ferritin in sensitised animals In these animals the appearance of vesicles was a sign of liver parenchymal cell injury

The kidney biopsy did not show any evidence of an acute kidney disease Glomerular changes were however far advanced from normal The changes found can be due to rheumatoid arthritis or to the complication of the therapy

The reaction seems to show that patients with a history of drug allergy are not always suitable subjects for successive osmium tetroxide synovectomies

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With the present volume, the 17th since 1955 Acta Rheumatologica Scandinavica will cease to appear under its present name and the publication will pass from Stemsviks Bokforlag to The Almqvist & Wiksell Periodical Company Under its new name the SCANDINAVIAN JOURNAL OF RHEUMATOLOGY it will continue to promote and publish advancements in the field of rheumatology

As we reach the end of our activities as publishers of Acta Rheumatologica Scandinavica we the management of Stemsviks Bokförlag wish to extend our gratitude to everyone who has helped us in our work Looking back we must necessarily call to mind the unselfish work given to the newly started journal in rheumatology by Professor Gunnar Edstrom who thus helped us to give it its high scientific standard His work has been continued during the last few years in the same manner by Professor Veikko Laine whom we also wish to thank During the entire existence of Acta Rheumatologica Scandinavica we have also had the privilege of the much appreciated collaboration of Doctor Olle Lovgren as the medical specialist most closely concerned for the actual preparation of each issue

Apart from these persons mentioned we also thank all the members of the editorial committee and other members of the Scandinavian Societies of Rheumatology who in any manner have been concerned in the preparation of the journal and to all contributors during the years who through their papers have helped us to keep our journal on a high scientific level

Last but not least we also wish to thank all our subscribers through whose support we have been able to continue the publication of Acta Rheumatologica Scandinavica during these 17 years

for Stemsviks Bokforlag AB

Ornulf Tonsberg

In 1954 an agreement was reached between the Scandinavian Society for Rheumatology and Steinsviks Bokforlag, publishers in Stockholm to start a new medical journal Thus the first issue of Acta Rheumatologica Scandinavica was published in 1955 under Chief Editor Gunnar Edstrom and Dr Olle Lovgren This was only possible through the generosity and confidence of the late Bjarne Steinsvik

The present volume no XVII will be the last of Acta Rheumatologica Scandinavica The Scandinavian Society for Rheumatology regretting the inconvenience caused to the publisher by this type of special journal proposed to terminate this contract During the spring of 1971 an agreement was reached that Acta Rheumatologica Scandinavica will terminate after Volume XVII The Scandinavian Society for Rheumatology made an agreement with the Almqvist & Wiksell Periodical Company Stockholm to commence publishing the Scandinavian Journal of Rheumatology (Acta rheumatologica scandinavica) with Volume I in 1972 under the same editorial staff as Acta Rheumatologica Scandinavica

The Scandinavian Society for Rheumatology wishes to express its gratitude to the publishing house Steinsvik for its generosity shown during our co-operation Special thanks go to Mr Gunnar Petterson who during these years has been mainly responsible for the technical editing of our journal

The Society takes this opportunity to thank all those who have given their contributions to our Acta amongst them authors redactors and referees We also thank our subscribers and readers

Acta Rheumatologica Scandinavica will remain in the history of Scandinavian medicine as a pioneer It will be followed by the Scandinavian Journal of Rheumatology which we hope will successfully continue the traditions of its predecessor

Veikko L Laine
Editor

Rombouts J J & Rombouts Lindemans C Acta Rheum Scand 17 248—267 1971

From the Rheumatism Foundation Hospital
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INVOLVEMENT OF THE HIP IN JUVENILE RHEUMATOID ARTHRITIS*

A Radiological Study with Special Reference to Growth Disturbances

By

J J ROMBOUTS** and C ROMBOUTS LINDEMANS***

Summary A retrospective radiological analysis of hip involvement in *juvenile rheumatoid arthritis (JRA) in 137 patients is presented*

When hip involvement occurs up to the age of fifteen (113 cases) growth disturbances are frequent and their aspects are varied The emphasis is put on the radiological study of these growth abnormalities In this group of patients, dislocation and subluxation of the hip is a *common feature Acetabular protrusion was only seen as a late* complication After the age of fifteen (24 cases) hip disease in JRA does not differ from the adult cases

The radiological aspects of articular involvement in juvenile rheumatoid arthritis (JRA) have been well studied (15 25 29) The relatively late destruction of articular cartilage and bone and the frequency of regional growth disturbances are two of the most characteristic features of arthritic joint involvement during childhood

The hip joint is a weight bearing joint in which anatomical deformities are of great importance On the other hand the growth process of this

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joint is complex and recent advances have been accomplished in the knowledge of the growth mechanism of the upper part of the femur (7 8 17 22 23 26) For these reasons the radiological changes affecting the involved hip in JRA are not only of practical but also of theoretical interest Few data have been provided on this subject except for the description given by Jacqueline et al (19) and for the recent study by Isdale (18)

Therefore a retrospective radiological study was undertaken of the hip involvement in a large series of patients affected by JRA with the emphasis on the analysis of the growth disturbances which develop owing to the disease process

MATERIAL

The records of 455 children with JRA treated at the Rheumatism Foundation Hospital of Heinola between 1951 and 1969 were studied All of them met the diagnostic criteria of JRA proposed by Ansell et al (2) The onset of the disease was prior to the age of 15 years included The female to male ratio was similar to that in previous investigations (14 21 25) 323 (70 8 %) girls and 132 (29 2 %) boys

Of these patients 154 (34 %) had involvement of one or both hip joints the distribution between males and females being identical with the group on the whole 116 females and 38 males This incidence of hip involvement is similar to that found by Sairanen (29) Martel et al (25) Delbarre (10) and Isdale (18) but lower than in Streda s and Bardfeld s (33) investigation and much lower than in the investigations by Jacqueline et al (19) and Shands and Muebe (31)

Because of inadequate radiological data 17 patients were omitted and this study therefore is based on 137 cases

CLINICAL DATA

Of these 137 patients hip involvement was bilateral in 118 and unilateral in 19 The sex ratio was 4 females to 1 male when the hips were involved bilaterally and 2 females to 1 male in the cases affected unilaterally When considering the cases with unilateral involvement only 10 out of 19 patients suffered from mild rheumatoid disease, but the follow up





Fig 1 A Localized erosion changes of the external part of the capital femoral epiphysis
Fig 1 B Same patient eight years later after the end of the growth Growth defect of the femoral head

in the 9 other cases did not exceed one year Therefore no conclusions could be reached

It may be seen in table I that hip involvement occurred in 113 cases up to the age of 15 and in 24 cases at a later age

RADIOLOGICAL FINDINGS

A Hip Involvement Starting up to the Age of 15

1 *Soft tissue swelling*

In JRA soft tissue swelling is the first abnormality and this is followed by osteoporosis (3 25) In the hip joint classical soft tissue signs have been described in septic arthritis (16) or in transient synovitis (II) These signs are not evident in RA (27 38) Recently Weston (38) has suggested that in RA the synovial mass in the hip joint lies mostly on the under surface of the femoral neck and that it can be demonstrated in the axial view during conventional radiography of the hip In this study only antero-posterior views were available and so no analysis of soft tissue swelling was done

2 *Osteoporosis*

This is usually an early sign of joint involvement in JRA but the objective evaluation of this manifestation proved difficult It did not however always manifest itself as the very first sign of hip involvement especially in very young patients where sometimes overgrowth of the femoral head or increased width of the joint space first attracted the attention

3 *Erosions and destructive changes*

According to previous authors erosions in JRA do not occur frequently at an early stage of the disease (29) particularly in the youngest children (21) This was also found by Jacqueline et al (19) as far as the hip is concerned In severe cases of JRA epiphyseal destruction in metacarpal and metatarsal bones has been described by Forestier et al (13) Martel et al (25) Laurin and Favreau (24) and Laaksonen (21) According to Jacqueline et al (19) epiphyseal destruction in the hip is rare even in severe cases of many years duration They consider that the small bone volume is most often due to disturbances of growth Martel et al (25) have interpreted these changes as being compression fractures of the epiphysis

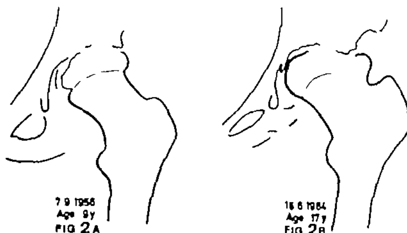


Fig 2 A Drawing of fig 1 A
Fig 2 B Drawing of fig 1 B

TABLE I

Age at the onset of the disease	Age at the onset of the hip involvement 0—3	4—9	10—15	Total up to 15	Total over 15
0— 3	10	17	2	29	—
4— 9	—	31	23	54	6
10—15	—	—	30	30	18
Total	10	48	55	113	24

In this study erosions were not observed prior to the second year of hip involvement *in children under four years at the onset of the involvement* of the hip Three among the ten affected patients had erosions after four years of hip involvement

In the other two groups (4—9 y and 10—15 y) erosions may occur after the first year of hip involvement in 15 % and 30 % of the cases respectively At long term follow up erosions are often present (more than 80 % after 10 years of evolution) Furthermore in those cases of long lasting hip disease, erosive changes due to the rheumatoid process may be very severe 5 cases 9 to 14 years after the onset of hip involvement

On the other hand massive resorption of the femoral capital epiphysis by granulomatous synovium has not been observed up to 15 years of age But localized pannus lesions of the capital femoral epiphyseal ossification centre may produce important growth disturbances of the femoral epiphysis leading to flattening of the femoral head or loss of sphericity of the femoral head (16 cases) One such case is shown in fig 1 and the evolution is redrawn in fig 2 In fig 3 the evolution of another case is shown it can be seen that the area of massive bone loss does not correspond to the weight bearing portion of the femoral head It therefore seems difficult to interpret these findings as being related to compression fractures only

In JRA roentgenological healing of erosions has been described to occur For Knutsson (20) it consists of a cortical covering transforming an erosion into a deformity Laaksonen (21) described correction of erosions in the joints of the hand in 19 cases but in some of these cases she found complete healing of the erosion without deformity of the bone

In this series cortical covering of destructive changes was found in some cases of hip disease mostly simultaneously to the development of osteoarthritic changes We have not seen any restitutio ad integrum It must be considered that in the hip joint particularly in the young child the articular cartilage is very thick and when the erosive changes are seen roentgenologically they are already severe On the other hand the hip is a weight bearing joint in which secondary osteoarthritic changes appear early

4 *Narrowing of the joint space*

It has been stated that narrowing of the joint space is not an early sign in JRA (15 21 5 29) and particularly in hip involvement (19)

In the present investigation it is seldom seen after one year of hip involvement for patients under seven years of age in (7/23 cases) After the age of seven it is seen after one year in 25 % (2 5 cases) and after five years of follow up in 75 % of the cases (6 cases) The narrowing often remains slight but ankylosis has ensued in 15 hips of which three hips presented complete bony ankylosis At the time of the development of ankylosis the youngest patient was 12 all the others were more than 15 years old

A rare evolution has been seen in four hips in which there was some restoration of joint space together with development of secondary degen

Fig. 3 *A and* 3 *B* Evolution of another case with localized erosive changes

Figs 4 *A and* 4 *B* Some restoration of joint space occurs together with development of secondary degenerative changes





Fig 5 A Overgrowth of the right femur Right knee and hip are involved *Fig 5 B* Pure overgrowth Coxa valga and acetabular insufficiency Same case as in fig 5 A

erative changes as shown in fig 4 This has been reported previously for the hip by Ansell (3) and for small joints by Laaksonen (21)

5 *Growth disturbances of the upper part of the femur*

In 1956 Ansell and Bywaters (1) described the general and regional growth disturbances in JRA Abnormalities of bone development occur primarily near the affected joints Furthermore it has been postulated that the closer an inflammatory process is to an epiphysis the greater is the disturbance in epiphyseal growth (37) In JRA periostal (9 13) and enchondral (13) ossification may be disturbed But regional growth abnormalities consist mainly of acceleration or retardation of epiphyseal development Those two features may appear at the same time or succeed one another and the end point will be a mixture of overdevelopment and underdevelopment Epiphyseal fusion is an important feature in this phenomenon thus epiphyseal fusion is often premature in JRA (1 21 25)

Growth of the upper part of the femur is complex The importance of

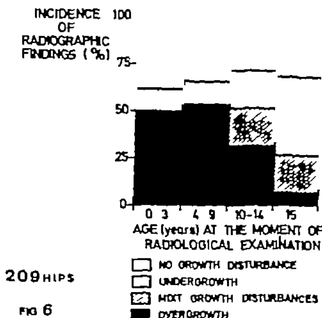


Fig 6

the cephalic and trochanteric growth plates has been well studied clinically and experimentally (7 8 17 22 23 26) If the two growth plates are not symmetrically influenced overgrowth or undergrowth are followed by architectural abnormalities Dominance of the cephalic growth plate gives rise to lengthening and valgus of the femoral neck and to longitudinal overgrowth of the femur (Fig 5) Whereas dominance of the trochanteric growth is followed by varus of the femoral neck The femoral capital epiphyseal ossification centre and the cephalic growth plate are related to the synovium of the hip because of anatomical and vascular (34) features The trochanteric growth plate is more independent Furthermore these changes cannot be ascribed only to the increased blood flow of inflammation It is obvious that mechanical (30 35) neuromuscular (?8) and hormonal factors influence the growth of bones

In this investigation abnormalities of development of the upper part of the femur occurred and showed varying aspects Growth disturbances in the upper part of the femur were frequent (Fig 6) The frequency of overgrowth and undergrowth was related to the age of the patient and to the duration of hip involvement at the time of radiological examination



Fig 7 Pure undergrowth The femoral head is lodged in disproportionately large acetabulum JRA set in at the age of three amyloidosis followed at the age of ten This patient died at the age of twelve

In the young child (before the age of nine) overgrowth is more common than underdevelopment The most common feature of overgrowth is the overdevelopment of the femoral head — coxa magna This may happen rather early in most of the cases within two years of evolution In this group coxa magna is usually associated or followed by overgrowth of the femoral neck namely by lengthening and valgus (Fig 5) Prior to the age of nine underdevelopment of the femoral neck and head was only seen in the most severe form of the disease (5 cases)

In children between nine years of age and epiphyseal fusion overdevelopment remains frequent but there is often a mixture of overdevelopment and underdevelopment A frequent finding is coxa magna associated with varus or shortening of the femoral neck (Fig 12 A and fig 13 A) Pure underdevelopment is also seen in severe cases (Fig 7)

Normally fusion of the cephalic epiphysis occurs between the seventeenth and the twentieth year (5 32) males from 18 to 20 years (5) females from 17 to 19 years (5) In the study of Jacqueline et al (19) premature fusion of the femoral capital epiphysis occurred between the age of 10 and 14 years In this series the radiographs of the hips taken

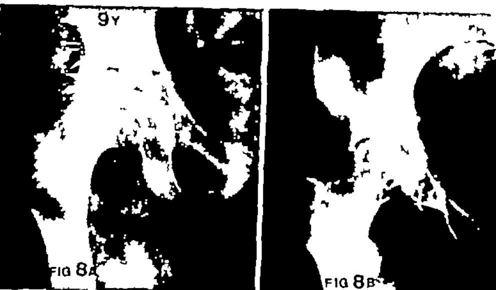


Fig 8 A At the age of nine some overdevelopment of the femoral head *Fig 8 B* Same case at the end of the growth underdevelopment has resulted

between the ages of 10 and 13 showed premature fusion in 45 % of the cases (18 cases) In the radiographs of the hips taken between 14 and 16 years premature epiphyseal fusion was present in 75 % of the cases (22 cases) The fusion is sometimes faulty

If one considers the radiological appearance at the end of the growth it is found that in many patients who have shown overgrowth of the upper part of the femur at some period during childhood growth stops *earlier than usually particularly if premature fusion of the epiphysis* occurs The final result may be underdevelopment (Fig 8) Most often however it is a mixture of overdevelopment and underdevelopment

Pure overdevelopment (Fig 5 and fig 9) is seen *in two conditions* When the hip involvement started at an early age and the inflammatory process becomes inactive during the latter years of growth (2 cases) — and when the involvement starts just prior to the end of the growth period (5 cases)

Association of overdevelopment and underdevelopment is most often seen if the involvement started between the ages of 9 and 14 In these cases (Fig 12 A and fig 13 A) growth abnormalities are usually mod



Fig 9 Coxa valga subluxans

erate in degree It may also be seen in earlier cases particularly if the involvement remains active at the end of the growth In these cases the morphological abnormalities may be very spectacular for example valgus position of the femoral neck which is short and thin a large lesser trochanter and abnormalities of the greater trochanter These manifestations are generally combined with important abnormalities of the acetabulum often with hip dislocation (Fig 10 and fig 11) On the other hand harmonious underdevelopment of the femoral head and neck and acetabulum have been observed even in cases which had transient roentgenological signs of overgrowth (8 cases)

6 *Articular congruity*

Growth disturbances of the upper part of the femur are generally associated with growth abnormalities of the acetabulum Overgrowth with valgus of the femoral neck disturbs the ossification of the lateral part of the acetabulum and leads to acetabular insufficiency (Fig 5 and fig 9) Coxa magna alone or overgrowth of the femoral head associated with slight varus of the femoral neck may be matched by a large acetabulum (Fig 12 A and fig 13 A) Localized epiphyseal abnormalities are associated with a mirror deformity of the acetabulum (Fig 1 B and fig 2 B) The underdeveloped head of the early childhood type is lodged in a







Figs 10 A B and C Evolut on of a case of pathological hip dislocation



Fig 11 A Extrusion at the ge of fourteen *Fig 11 B* Same case four years later showing hip dislocation

disproportionally large acetabulum (Fig 7) however the small head of the adolescent type is well covered in an underdeveloped but adapted acetabulum

Hip dislocation and acetabular protrusion are the two extreme features

a Dislocation or Subluxation of the Hip

Vainio and Sairanen (36) have published an important series of pathological hip dislocations in JRA This complication has also been studied subsequently by Forestier et al Jacqueline et al Grokoest et al and Martel et al According to these authors (13 15 19 25) joint effusion and relaxation of ligamentous and capsular structures are the primum movens of sudden luxation Muscular foreshortening due to fibrosis may also play a role (25) Widening of the joint space by effusion or granulomatous synovium is the mildest manifestation The progressive dislocation or subluxation by growth disturbances must also be considered

In this series widening of the joint space with lateral shift of the femoral head in the acetabulum was seen in 32 hips (in 26 % of the cases prior to the age of nine and only in 3 5 % of the cases between 9 and 15 years of age) Dislocation was observed in ten patients or fifteen hips

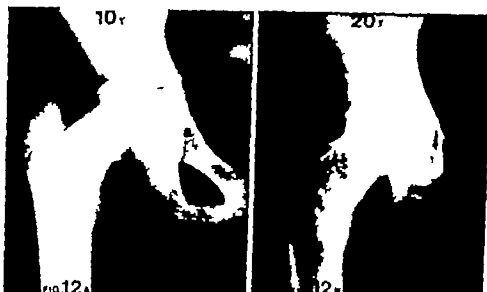


Fig 12 A Slight overgrowth of the femoral head associated with moderate varus position of the femoral neck (1?0) *Fig 12 B* Same case ten years later acetabular protrusion has ensued

In seven hips the dislocation occurred rapidly (Fig 10) the youngest patient was 3 years old, the oldest was 13 In five hips, minor extrusion was detected early but the dislocation occurred over a period of years (Fig 11) simultaneously with growth disturbances In three hips the mechanism of dislocation is unknown

Subluxation (Fig 5 B and fig 9) was seen in fifty hips

It is interesting to note that all of the ten patients with a hip dislocation developed their rheumatoid disease prior to 1956 Later cases in this series did not reveal any further instance of this extreme complication It is not known whether this finding has any bearing to the more wide spread use of more potent anti inflammatory agents corticosteroids excluded as a rule in this disease since about that time

b Encirclement and Acetabular Protrusion

Acetabular protrusion is a well known complication of hip involvement in adults (12) In the literature there are few references to protrusion during the evolution of JRA Sairanen (29) has published six cases of

Fig 13 *A* Bilateral encirclement *Fig* 13 *B* Same case, four years later acetabular protrusion has ensued



Fig 14 A and B Development of osteoarthritic changes

acetabular protrusion (5 bilateral cases and 1 unilateral case) but the radiological examination was performed after the age of 15 Jacqueline et al (19) consider that the tendency to subluxation distinguishes the hip involvement in childhood from that in the adult which on account of its destructive processes, causes a secondary protrusion Nevertheless they noticed a tendency to encirclement in mild cases of involvement which started between the age of 8 and 14 years In this study in 14 cases (26 hips) an overdeveloped head was encircled by an overdeveloped acetabulum The femoral neck was normal or was slightly short or in varus position This was seen only in children who developed hip disease between 9 and 15 years of age Four of these cases (8 hips) were followed *beyond the end of growth All of them developed an acetabular protrusion* before the age of 20 years Two such cases are shown in fig 12 and in fig 13

7 *Osteoarthritic changes*

Osteoarthritic changes are found to occur at the end of growth particularly in those cases where the inflammatory changes have diminished or have even disappeared (Fig 14) Nevertheless osteoarthritic lesions do not imply definite healing of a hip disease because it has been seen that the inflammatory process may reoccur several years later

B Hip Involvement Starting after the Age of 15

Clinical and radiological aspects do not differ significantly from the adult cases Inflammatory changes appear early particularly narrowing of the joint space Osteoarthritic changes may appear early (7/24 cases) Acetabular protrusion is often seen even in youth (4 cases respectively at the age of 18 20 27 and 29 years)

Morphological abnormalities may be seen for example lengthening of the femoral neck (2 cases) shortening of the femoral neck (2 cases) undergrowth of the femoral head (1 case)

Hip involvement may begin long after the onset of the rheumatoid disease

CONCLUSIONS

In JRA when hip involvement occurs during the growth the following points can be made

1 Osteoporosis is an early sign whereas erosions and narrowing of the joint space appear at a later stage of the disease In case the rheumatoid process affecting the hip remains active for a long time erosions and narrowing become severe Furthermore localized inflammatory lesions of the capital femoral ossification centre may produce important growth disturbances of the femoral epiphysis

2 Growth abnormalities are frequent and their aspects may vary during the evolution In young children overgrowth in the upper part of the femur is common but underdevelopment or the association of overdevelopment and underdevelopment are more often seen as the child gets older and the involvement of the hip lasts a longer time At the end of the growth underdevelopment is more frequent than overdevelopment similar observation has been made by Ansell and Unlu (4) Growth disturbances are associated with architectural changes (valgus or varus of the femoral neck) which are thought to be related in most of the cases either to a dominance of the cephalic growth plate either to a dominance of the trochanteric growth plate secondary to the rheumatoid disease

3 Acetabular abnormalities are related to the deformities of the upper part of the femur Pure overgrowth with valgus position of the femoral neck leads to acetabular insufficiency In these cases surgical correction of the valgus during the growth may be suggested as it was proposed by Cauchoix et al (6) in overgrowth of the hip due to tuberculosis But it

has been shown in this study that pure overgrowth persists rarely Such surgery may be of value only in the cases in which the inflammatory process has become and will remain inactive This latter point is difficult to ascertain

4 Widening of the joint space and lateral shift of the femoral head are the first stages of hip dislocation In these events classical drug therapy should be associated with conservative orthopedic treatment as it was proposed by Vainio and Sairanen (56)

5 Acetabular protrusion is not a classical complication of hip involvement during childhood But it was noticed that when an overdeveloped head was encircled by a large acetabulum and the femoral neck was normal or slightly in varus position the outcome at the end of the growth was acetabular protrusion

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MYCOPLASMA IN JUVENILE RHEUMATOID ARTHRITIS

By

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Summary Two cases of juvenile rheumatoid arthritis (JRA) with a positive mycoplasma isolation from synovial fluid are presented The second patient, who was seen when the disease was in an early stage, had antibodies against an isolate from RA and also a T strain mycoplasma from nongonococcal urethritis

If an infection is suggested as possible cause of RA the etiologic agent should be recovered at an early stage of the disease e g in sick children In our laboratory a mycoplasma was isolated in three cases of JRA one of whom was included in a previous series (3) The other two are presented here

METHODS

Isolation Technique The medium used was the solid and diphasic PPLO medium described by Marmion (5) with the following modifications 1 Brain heart infusion broth was used instead of PPLO broth for solid medium 1 1 per cent agar was added to it 2 The broth medium was further enriched with egg yolk pasteurized at + 60 C for 50 min and added in amounts of 0 1 ml to 10 ml of broth medium 0 3 ml of undiluted synovial fluid was inoculated into 3 ml of

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enriched brain heart infusion broth The broth cultures were incubated at + 37 C and subcultures were made on solid media after 10 and 20 days inoculating 0 1 ml on small Petri dishes five cm in diameter The agar plates were incubated in an anaerobic milieu at + 37 C for 10 days Then they were examined for growth as described earlier (4)

Preparation of Hyperimmune Sera The origin of the mycoplasma strains the antigen preparation and the immunization procedure have been described elsewhere (1) In order to prepare antisera against the isolates these were grown in enriched brain heart infusion broth with pasteurized egg yolk 1 3 ml per 350 ml of broth and incubated for 15—20 days For intravenous injections a 100 fold concentrated antigen was used

Biochemical and Growth Inhibition Tests These were described earlier (4)

Antibody Studies Indirect hemagglutination (IHA) technique was used as reported elsewhere (4)

RESULTS

Isolation Studies In both cases tiny colonies resembling mycoplasma were seen in the primary culture in large numbers in the second case The colonies were very tiny about 1/10 to 1/100 of the large colony mycoplasma However with Dienes stain and an oil immersion lens the fragile granular structure could be clearly seen The figure illustrates the microscopic appearance of the strain recovered from the synovial fluid in the first case

The isolated strains did not convert to bacteria when penicillin and thallium acetate were omitted from the culture medium They required sterol for their growth

Biochemical Studies The isolates were both arginine positive They did not ferment glucose or split urea.

Growth Inhibition Studies The antisera against the two isolates inhibited the growth of M arthritidis and strain 20 P with a very narrow inhibition zone of 2—3 mm M hominis M salivarium and M orale type 1 were not inhibited Strain 20 P was isolated in 1964 in our laboratory from the synovial specimen of a woman with RA (1)

Antibody Studies Measured by the indirect hemagglutination technique no antibodies could be detected in the patients sera against M



Fig. Strain 302 M 1st passage isolated from the synovial fluid in RA. 1 000 fold magnification.

arthritidis and strain 20 P. However, the second patient had an antibody titer of 1 024 against another isolate, 176-M, from RA (4). She also had antibodies in a titer of 512 against strain 71 T. This strain was cultivated in our laboratory from the urethral specimen of a male with nongonococcal urethritis (2).

CASE HISTORIES

Case 1. L. T. A 10-year-old girl who since 1964 had stiffness and pain in her thoracal spine with restricted movements. From April 1965 her left ankle was swollen and painful and from the end of the same year there was hydrops in the right knee.

In May 1966 she was admitted to the ward. Movement was restricted in the thoracal spine, left ankle and both knees, the right knee was much thicker than the left. The ESR was 41, hemoglobin 12.4 g, AST 360, ASTA 2.8, Waaler Rose — (32), Latex —, antinuclear antibodies were negative. The immunoglobulins, especially IgG, C' and alpha hap-

toglobin were increased The histologic finding of a synovial specimen from the right knee was compatible with RA The x ray changes of both ankles and knees were also similar to those seen in this disease Dg JRA On May 27 thymectomy was performed The girl was then treated at the Rheumatism Foundation Hospital at Heinola

From spring 1969 the patient s left knee was swollen and painful On Sept 3 a punction and extirpatio menisci med genu sin were performed 45 ml of yellowish fluid were obtained A mycoplasma was isolated from the fluid and synovial specimen

Case 2 N B A previously healthy girl aged 2 who in January 1970 complained of pain in her right hip so bad that she limped The right knee became swollen and painful

She was admitted to the hospital on Feb 14 The ESR was 45 hemoglobin 10 g, Waaler Rose — Latex — AST 50 ASTA 1 0 direct Coombs test — cryoprecipitins — antinuclear antibodies (FA) total titer 1 320 IgG 1 320 IgM 1 5 and on March 25 total titer 1 1 280 IgG 1 1 280 IgM 1 20

On Feb 16 punction in the right knee was done No bacteria were cultivated and the culture for tuberculosis was also negative Instead a mycoplasma was isolated The histologic finding for the synovial specimen was compatible with RA X ray arthrography revealed minor synovitis like changes The patient was moved to the Rheumatism Foundation Hospital at Heinola She had there also an iritis Dg Probable JRA

DISCUSSION

The first of these two patients had a five year history of the disease the second was seen in an early stage of RA In both cases a mycoplasma was cultivated from the synovial fluid but only the latter showed mycoplasma antibodies This indicates that mycoplasma probably continues to exist in joints for several years when the disease process remains active and that by then it is possible that no antibodies can be detected by the conventional serologic methods

It is interesting that the second patient had mycoplasma antibodies against isolate 176-M from RA and 71 T *from* nongonococcal urethritis (NGU) However nothing suggested that the patient s illness was an uropolyarthritis Using the latter antigen and *IHA* technique 24 per cent

of 54 patients with NGU showed serologic evidence of a recent infection with T strain mycoplasma (2) This indicates that mycoplasma isolates from these two diseases probably share common antigens This poses the question of a possible genital transmission of RA or in its juvenile form an infection caught at the birth

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TRIAMCINOLONE HEXACETONIDE FOR INTRAARTICULAR AND INTRAMUSCULAR THERAPY

By

SVEND CLEMMESEN

Summary Triamcinolone hexacetonide has been used in 133 patients in various series for intraarticular and intramuscular therapy to elucidate the possible universal effect and the duration of the local effect The results seem promising

Since 1966 triamcinolone hexacetonide (Aristospan) (TH) has been used in the Department of Physical Medicine and Rheumatology of Kommunehospitalet for intraarticular therapy

In addition to reports of Hollander (2, 3) Hume Kendall (4) and del Vallado et al (5) our summarized results may be of interest Triamcinolone hexacetonide is much less water soluble than triamcinolone and therefore provides a prolonged duration of action when administered intraarticularly or intramuscularly Five trials involving a total of 133 patients were conducted

Experiment No 1
(12 patients)

The purpose was to determine if an effect on blood sugar serum sodium serum potassium and the 17 ketogensteroids could be demonstrated when TH was injected intraarticularly into knees with hydrops of various origin (Six patients with osteoarthrosis of the knees and six patients with rheumatoid arthritis) Measurements were made before

the injection two weeks after the injection and four weeks after the injection

The dose of TH injected was 20 mg in one case 65 mg in one case 120 mg in one case 80 mg in two cases and 40 mg in seven cases

RESULTS

1) No effect was found on blood sugar serum sodium and serum potassium but in most cases a slight increase of the 17 ketogensteroids could be seen (but still within or at the border of the normal range)

2) The clinical effect on the joint swellings and joint fluid was excellent Even in joints with chronic swelling of the capsule and chronic fluid accumulation the swelling fluid and pain disappeared after 3—4 days and *the effect persisted for 3—4 weeks* in the inflammatory joints (RA) whereas the effect on simple hydrops in osteoarthrosis was persistent

3) In six patients x rays were taken of the knees 6—12 months after the injection and no damage was found Brånemark et al (1) have described disturbances in synovial microcirculation by sorbitol However this should not be harmful or cause any damage of the cartilage The cartilage is not influenced by sorbitol or by steroids We have never observed any damage Only direct injection into the cartilage is harmful and can be avoided by good technique

Experiment No 2
(20 patients)

The purpose was to determine the average duration of clinical effect in 20 patients On the basis of experience in the first study the standard dose for intraarticular injections was 40 mg The effect was remarkably good one week after injection with few exceptions On an average *the duration of effect of each injection was 10 weeks* after which another injection was needed

The 20 patients included nine patients with arthrosis genuum five with RA two with gout one with traumatic hydrops one with tennis elbow one with hygroma and one with psoriatic arthropathy

Experiment No 3
(48 patients)

The purpose was to study the routine intraarticular and intramuscular use of TH The patients were grouped as follows

Group I

a) 19 patients with osteoarthrosis of the knees without hydarthrosis
b) 4 patients with osteoarthrosis of the knees with hydarthrosis
c) 5 patients with traumatic hydarthrosis
d) 2 patients with RA without hydarthrosis
e) 2 patients with RA with hydarthrosis

The standard dose given to these patients was 40 mg TH which was injected into the articular capsule of the knee between the tendon of the quadriceps muscle and the tractus iliotibialis tendon (at the thin part of the capsule)

Group II

a) 4 patients with lumbar muscular fibrositis
b) 5 patients with gluteal muscular fibrositis
c) 3 patients with muscular fibrositis of the levator anguli muscle

The standard dose given to these patients was 20 mg TH mixed in the syringe with 5 ml of 2 % procaine with adrenalin

Group III

a) 1 patient with tenosynovitis crepitans at the flexor tendon of the hand
b) 1 patient with bursitis olecrani
c) 1 patient with a tennis elbow
d) 1 patient with a ganglion manus

The standard dose given to these patients was 20 mg TH

There was a good effect on osteoarthrosis of the knees with hydarthrosis in four cases and a good effect on osteoarthrosis of the knees without hydarthrosis in 19 cases Muscular fibrositis was treated with injection in nine cases with a good effect. Follow up examination was made of 25 patients two months later while 16 patients did not come back, presumably owing to a good effect (since the patients were told to report if the effect was not satisfactory)

The rapid and lasting effect of 40 mg TH given intraarticularly in osteoarthrosis of the knees with painful periarticular fibrositis with or

without hydrops has been confirmed In 20 % of the cases the large dose of 40 mg caused a moderately painful reaction for 24—48 hours However later complications have not been observed and only in 11 cases was it necessary to repeat the injection after approximately two weeks Secondary cartilage destruction was not observed

Experiment No 4
(43 patients)

The purpose was to compare the effects of intraarticular injection of 40 mg TH and 30 mg Celestone Chronodose (betamethasone disodium phosphate and betamethasone acetate consisting of betamethasone 3 0 mg as disodium phosphate in solution and betamethasone acetate 3 0 mg in suspension)

The patients were grouped as follows

Group I

Nineteen patients with osteoarthrosis of the knees with capsular swelling and pain (five with fluid in the joint) were given *30 mg Celestone Chronodose* with an *average duration of effect of 3—4 weeks* One week after the effect of this drug had worn off *40 mg TH* was given in the same joint with an *average duration of effect of eight weeks*

The injections of TH were repeated 2—6 times

No side effects were seen with either of the preparations All the injections were given in the suprapatellar pad just above the upper border of the patella behind the quadriceps tendon and in front of the tractus tendon

In a few patients slight pain and swelling appeared during the first 24 hours (In a few patients not included in this trial injections were given directly into the thick fibrous capsule by mistake resulting in painful reactions but never necrosis)

Celestone Chronodose often gave a relieving effect within 24 hours because of the rapid resorption of phosphate

Group II

Similar studies have been done in eight patients with RA, who were given *30 mg Celestone Chronodose* in the knee with an *average duration of effect of three weeks*

A week later 40 *mg* TH was given in the same joint, with an *average duration of effect of nine weeks*

The injections of TH were given 1—3 times

Group III

Two patients with tennis elbow one patient with gout and one patient with fluid in the knee were given 30 *mg Celestone Chronodose with an average duration of effect of four weeks* A week later 40 *mg* TH was given in the same joint with an *average duration of effect of 9—10 weeks* The injections of TH were given only once

Group IV

Eight patients with osteoarthrosis in the knees were given 40 *mg* TH (and no Celestone Chronodose) *The average duration of effect was eight weeks* The injections of TH were given 1—3 times

Group V

Two patients with distorsion (tennis elbow) one patient with hygroma and one patient with LBD were given 40 *mg* TH (and no Celestone Chronodose) *The average duration of effect was seven weeks* The injections of TH were given 1—5 times

The previous observation of a long lasting effect of TH was confirmed in this series of 43 patients While injection of Celestone Chronodose had an effect lasting 3—4 weeks TH usually proved effective for at least eight weeks This is longer than that reported by some other investigators and may be explained by the higher dose used in this study Even with these high doses harmful side effects were not observed

Experiment No 5
(10 patients)

The purpose was to investigate the possibility of replacing a peroral dose of steroid by an intramuscular injection of 100 mg TH In ten patients with RA maintained on a moderate dosage of betamethasone or prednisone this therapy was replaced by one intramuscular injection of 100 mg TH

In one case no systemic effect was observed while in the others the duration of TH effect before peroral treatment had to be resumed was ten days in one case two weeks in three cases three weeks in three cases, five weeks in one case and six weeks in one case

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THE TOTAL COMPLEMENT ACTIVITY OF SYNOVIAL FLUID IN JUVENILE FORMS OF ARTHRITIS

By

H Hedberg

Summary The total complement activity of synovial fluid was determined in 47 patients with various forms of juvenile arthritis The lowest complement values of the synovial fluid were found in patients with juvenile rheumatoid arthritis (JRA)

The significance of various correlations in JRA — the complement activity of synovial fluid correlated inversely with both the age at onset and the rheumatoid factor titres — with regard to pathogenesis and the possibility that juvenile as well as adult RA might be a heterogeneous group of diseases remains obscure Observations made support the idea that oligo-arthritis is a cond tion essentially distinct from RA.

As in the case of adult rheumatoid arthritis (RA) interest in juvenile RA has focused on the complement (C) activity of the synovial fluid, although the series have been small and sometimes amalgamated with series of adult RA (4 5 6 7) In a mixed series of RA consisting mainly of adult RA and only to a minor extent of juvenile RA the synovial fluid C activity varied inversely with the rheumatoid factor (RF) titre (6)

Juvenile RA differs markedly from adult RA in the frequency of positive RF tests which is much lower in juvenile RA This refers to conventional RF tests such as Waaler Rose latex and F II tests not the

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TABLE I

Clinical and Laboratory Data in 47 Patients with Various Forms of Juvenile Arthritis

	Rheumatoid arthritis			Oligo arthr	Psor arthr	Ankyl spond & Reiter's dis	Other non rheum arthr 1)
Age at onset (yrs)	1—5 (3) 2)	6—10 (8)	11—16 (13)	2—15 (9)	—10 (5)	9—16 (11)	2—15 (10)
No of cases	6	8	10	1		5	1
Mean duration of disease (yrs)	8	6	4	4	8	1	3
Examined after 16 years of age	2/6	1/8	3/10	1/1	1/	1/5	1/1
Effusion of < 3 months duration	0/6	1/8	2/10	2/1	0/	2/5	1/1
Mean ESR	40	38	18	20	21	60	71
Pos ASLT 5)	1/6	5/8	4/10	4/12	1/2	3/5	1/4
Pos ANF test	2/5	1/6	0/6	2/6	2/2	0/3	1/3
Pos SSC$_3$ test[4])	0/6	1/8	7/10	0/12	0/2	0/5	0/4
Pos Latex$_1$ test[4])	0/6	1/8	8/10	0/12	0/2	0/5	0/1
Pos Latex$_{SF}$ test[4])	0/6	1/8	8/10	0/12	0/	0/5	0/4
Mean WBCx10^3 per mm^3 synov fluid	25 (4) 4)	13 (5)	13 (6)	23 (6)	11 ( )	26 (3)	157 (3)
Corticosteroids or ACTH	4/6	/8	3/10	1/12	0/2	1/5	1/4
♂/♀	3/3	2/6	2/8	6/6	0/2	1/1	3/1

1) Atypical polyarthritis 3 patients (in associated with ulcerative colitis) septic arthritis one patient
2) Mean age at onset
3) See fig 3
4) No of cases examined
5) Antistreptolysin 0 titer

more sensitive test for anti IgG factors used by Torrigiani et al (12) In some reports dealing with juvenile RA attention has been called to the correlation between RF positivity (by conventional tests) and age at onset of the disease (2 3 11)

In view of the above mentioned relationships and in order to provide a better survey an extended series of juvenile arthritis patients was studied and the results are presented below

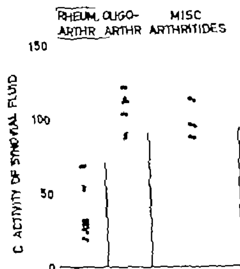


Fig 1 The total complement (C) activity of synovial fluid in 3 groups of juvenile arthritides one of rheumatoid arthritis (24 patients) one of oligo-arthritis (see ref 1) (12 patients) and one group of miscellaneous arthritides consisting of ankylosing spondylitis (3 patients) Reiter disease (2 patients) psoriatic arthropathy (2 patients) septic arthritis (1 patient) and atypical polyarthritis (3 patients in 2 of them associated with ulcerative colitis)

MATERIALS AND METHODS

The series consisted of 47 patients in whom joint symptoms had appeared before the age of 16 The patients were selected and classified essentially as described elsewhere (6) RA patients with positive RF tests were particularly looked for The term RA refers to a generalized arthritis (of the adult type) satisfying at least five criteria for the diagnosis definite RA (9) no subcutaneous nodules were observed in this series of RA patients In twelve patients with only a few joints affected the condition was labelled oligo-arthritis essentially according to Ansell & Bywaters (1) In three patients the arthritis was labelled atypical polyarthritis (see ref 7) the RF tests were negative in two of these patients polyarthritis was associated with ulcerative colitis Some laboratory and clinical data are given in table I

The techniques used for the determinations of RF titres antinuclear factors (ANFs) and the synovial fluid C activity have been described elsewhere (6) the latter activity was determined with a coefficient of

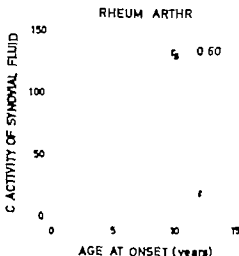


Fig 2 Relation between synovial fluid complement (C) activity and age at onset in 24 cases of juvenile rheumatoid arthritis
r_s = Spearman s rank order correlation coefficient

variation of about 10 % Both parametric and non parametric (10) statistical methods were used

RESULTS

The individual C activity of synovial fluid in three groups of juvenile arthritides is demonstrated in fig 1 In RA as a whole this activity was very significantly lower than in oligo-arthritis ($p < 0.001$) and significantly lower than in the miscellaneous group ($p < 0.01$) consisting of various other forms of RF negative arthritides not labelled RA

Within the group of juvenile RA the variation of the synovial fluid C activity could be related to the age at onset and to the RF titres (Figs 2 and 3)

As shown in fig 2 the synovial fluid C activity varied inversely with the age at onset ($r_s = -0.60$ $p < 0.01$) Fig 3 suggests that a similar inverse relationship exists between this activity and the RF titres in JRA with positive RF tests the C activity was very significantly lower than in JRA with negative RF tests ($p < 0.001$) Confining the comparisons to RF negative forms of arthritis the latter group (JRA with negative RF tests) showed lower C values of the synovial fluid compared with both

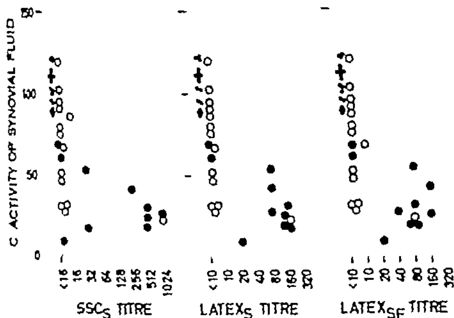


Fig 3 The total complement (C) activity of synovial fluid plotted against the RF titres

SSC$_s$ = the sensitized sheep cell test on whole serum

LATEX$_s$ = the latex agglutination test on the euglobulin fraction of serum.

LATEX$_{SF}$ = the latex agglutination test on the euglobulin fraction of synovial fluid.

— = sero-negative arthritis not labelled RA

O ∩ ● = juvenile RA with onset at 1 to 5 6 to 10 and 11 to 16 years, respectively

oligo-arthritis ($p < 0.001$) and the group of miscellaneous arthritides ($p = 0.02$) The latter two groups (Fig 1) differed only slightly in synovial fluid C activity ($p = 0.10$)

Except for the age at onset and the RF titres the synovial fluid C activity was not correlated to any of the parameters studied (see table 1) nor obviously to the intensity of synovitis or the type of current therapeutic measure Supplementary samples 16 altogether roughly agreed in C activity with those initially aspirated Patients with fresh or early effusion were too few to be considered

DISCUSSION

The characteristic sero-negativity in JRA was associated in most cases (2/3) with a synovial fluid C activity considered to be normal i.e.,

TABLE II

The Distribution of the Synovial Fluid Complement (C) Activity Values in Adult and Juvenile Rheumatoid Arthritis

RF tests[1]	Type of arthritis	No of patients	C activity of synovial fluid				
			<25	25—49	50—74	75—99	>100
Negative	Adult	32	5/32	1/32	8/3	13/32	5/32
	Juvenile	16	0/16	4/16	4/16	5/16	3/16[2]
Positive	Adult	101	47/101	37/101	14/101	2/101	1/101
	Juvenile	9	4/9	4/9	1/9	0/9	0/9

1) See fig 3 and ref (7)
2) One case added

with values from 56 to 140 (7) whereas in all sero positive JRA patients so far studied lower C values were found (Fig 3) The findings in adult forms of RA are practically identical as shown in table II This means that the well established difference in sero positivity between adult and juvenile RA is correlative to a similar difference in synovial fluid C activity In view of this association and the correlation in JRA between age at onset and sero positivity (2 3 11) the observation of an inverse correlation between age at onset and synovial fluid C activity (Fig 2) is merely confirmatory The significance of these relationships with regard to pathogenesis and the possibility that juvenile as well as adult RA might be a heterogeneous group of diseases is still obscure (7 8)

Recent data indicate that a depression of the synovial fluid C activity occurs in RA as often as RF positivity whereas RF negative arthritides other than RA and SLE (e g ankylosing spondylitis Reiter's disease and psoriatic arthropathy) generally show normal synovial fluid C values (7) In oligo-arthritis where the RF tests were negative in serum and synovial fluid (Fig 3) the synovial fluid C values were normal and essentially comparable to those found in juvenile forms of the RF negative conditions mentioned (Fig 1) Markedly lower C values compared with those in oligo-arthritis were found not only in JRA as a whole but also in JRA with negative RF tests ($p < 0.001$) These observations support the idea that oligo-arthritis ought to be considered a separate group distinct from RA

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RADIOGRAPHIC APPEARANCE OF THE PUBIC SYMPHYSIS IN OLD AGE AND IN RHEUMATOID ARTHRITIS

By

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Summary The radiographic appearance of the pubic symphysis was studied in 158 normal subjects of varying age and in 67 and 22 cases of RA and ankylosing spondylitis, respectively The pubic symphysis undergoes *significant anatomical changes during post adolescent life* In old age changes typical of osteoarthritic deformation are seen Small *local erosions are significantly more frequent in RA patients than in* the normal population Changes in ankylosing spondylitis tend to be more extensive and easily visible than in RA Tomographic studies suggest that minor changes typical of RA are often not revealed by ordinary radiography owing to the peculiar anatomical features of the symphysis

The pubic symphysis undergoes a distinct metamorphosis after puberty The various phases of its development have a definite relationship to age (5) As a result of his very extensive anatomical investigations Todd (5) was able to distinguish 10 different phases in the metamorphosis of the post adolescent symphysis from the age of 18 years to the age of 50 and upwards In his x ray studies Todd (6) also concluded that in subjects below the age of 40 undulating and irregular surface outlines indicate incompleteness of the process of development of the symphysial face On the other hand in older individuals an irregular outline indicates inhibited completion of the ventral rampart or frequently the occurrence of secondary erosion

The pubic symphysis may be severely affected in ankylosing spondylitis but in rheumatoid arthritis (RA) it is less frequently involved

TABLE I

Radio-Anatomical Features of the Pubic Symphysis of Non-Rheumatic Patients in Relation to Age and Sex

Sex and age	No. of cases	Upper edge: Uneven contour	Upper edge: Diff. in level	Upper edge: Prominent upper edge or lipping, Right	Upper edge: Prominent upper edge or lipping, Left	Joint gap: Mean width a	Joint gap: Mean width b	Joint gap: Mean width c	Joint gap: Asymmetry	Lower edge: Diff. in level	Lower edge: Prominent lower edge or lipping, Right	Lower edge: Prominent lower edge or lipping, Left
Females												
20—39	13	—	1	1	1	6	6	6	3	2	1	1
40—59	44	6	10	18	15	5	4	4	14	—	—	1
over 60	56	8	7	21	17	5	5	4	15	—	7	11
Males												
20—39	4	3	—	—	—	9	5	6	—	—	—	—
40—59	26	4	2	6	7	6	5	5	—	—	1	2
over 60	15	2	—	6	6	5	5	4	—	—	—	—

a = upper part of the gap b = central part of the gap c = lower part of the gap

(1). In addition the changes reported in RA are relatively mild. Owing to the wide normal variations in the appearance of the symphysis x-rays are only of limited usefulness in revealing whether this joint is affected in RA.

In the present study the radiographic appearance of the pubic symphysis in ordinary radiographs was analysed in normal material, in cases with RA and in ankylosing spondylitis.

MATERIAL AND METHODS

The normal material consisted of 158 consecutive cases of patients subjected to radiography of the pelvic region including the symphysis (intravenous pyelography, radiography of the pelvis or lumbosacral spine). These patients presented no clinical or radiographic evidence of arthritis. Only those radiographs that afforded a clear view of the symphysis were included. The joint space of the symphysis was measured at three points (upper, middle and lower part of the symphysial gap). Any difference in level between the upper edges of the pubic bones and any irregularity or asymmetry of the articulating bones

were noted Any abnormalities in the surrounding bone structure were also noted up to 2 cm laterally of the gap itself The various para meters studied are presented in tables I and II

The series of RA cases consists of 67 successively radiographed pa tients all of whom had both clinically and radiographically manifest signs of RA in the peripheral joints The radiographs of these patients were subjected to a similar study of the pubic symphysis Altogether 22 successive cases of radiographically manifested cases of ankylosing spondylitis were studied in a similar manner To obtain supplementary information about any minor changes in the pubic symphysis some elderly patients with and without rheumatism were subjected to symphysial tomography in the prone position

RESULTS

Radiographic Anatomy of the Pubic Symphysis in Relation to Age

The main radiographic features of the gross contours of the symphy sis in relation to age and sex are presented in table I The surface out line of the bony face of the symphysis was seen to undergo transforma tion being undulating and roundish in young individuals and straight in middle aged subjects In old age more numerous irregularities ap peared The extremities of the face did not appear complete until about the age of 40 Later on lipping of the symphysial margins appeared and resulted in x ray positive streaks along the margins of the symphys ial face often including osteophyte like prominences on the upper edge of the joint (Figs 1—3) These general features were identical in both sexes

The levels of the upper edges of the symphysis on the two sides differed occasionally in female subjects never in males In both sexes there were some exceptions to the usual pattern the symphysis retaining a distinct Y shaped contour of the upper edge Asymmetry was observ able more frequently in female subjects While osteophyte formations were frequent in the upper edge in subjects of both sexes over the age of 40 in the lower edge of the joint such prominences were only seen in some females over 60

The width of the symphysial gap showed a tendency of decrease with advancing age in both sexes The obstetric history was not avail able for all female subjects although it may have had some influence

TABLE II

Occurrence of Various Abnormal Changes in the Pubic Symphysis as Judged Radiographically

Patient group	Age	No. of cases	Upper edge: Diffuse erosion R	Upper edge: Diffuse erosion L	Upper edge: F R	Upper edge: F L	Joint gap and adjacent bone: Diffuse erosion R	Joint gap and adjacent bone: Diffuse erosion L	Joint gap and adjacent bone: E R	Joint gap and adjacent bone: E L	Joint gap and adjacent bone: Cyst R	Joint gap and adjacent bone: Cyst L	Lower edge: Diffuse erosion R	Lower edge: Diffuse erosion L	Lower edge: Fracture R	Lower edge: Fracture L
Non-rheum. females	20—39	15	2	2	—	—	1	1	—	—	1	1	—	—	—	—
	40—59	44	3	6	2	2	2	1	1	1	2	2	—	—	4	4
	over 60	56	10	11	1	2	2	5	—	1	3	3	—	1	—	—
Non-rheum. males	20—39	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	40—59	6	1	1	—	—	—	—	—	—	—	—	—	—	—	—
	over 60	15	—	—	—	—	1	1	—	—	1	1	—	—	—	—
RA females	20—39	9	1	1	—	1	—	1	—	—	—	—	—	—	—	1
	40—59	16	4	4	3		—	1	—	—	1	1	—	1	1	1
	over 60	31	7	9	9	7	—	—	8	5	3	3		—	5	5
RA males	20—39	3	—	1	—	—	—	—	—	—	—	1	—	—	—	—
	40—59	3	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	over 60	3	—	—	—	—	1	—	—	—	—	—	—	—	—	—
Ankyl. spondylitis both sexes	Fem. total	4	—	—		2	—	—	—	—	—	—	—	—	—	—
	Males															
	under 39	11	2	2	2		—	—	3	3	—	—	—	1	—	—
	40—59	4	—	—	—	—	—	—	—	—	1	1	—	—	—	—
	over 60	3	—	—	1	1	—	1	1	1	1	—	1	—	1	1



Figs 1—3 The appearance of the pubic symphysis at different ages in normal male subjects Fig 1 24 y symphysis with smooth undulating and roundish contour Fig 2 49 y fully developed extremities but no lipping The ventral rampart is visible as a dense area parallel to the articular margins Fig 3 65 y mild degenerative changes with lipping of the upper margin of the joint gap and prominence of the ventral and dorsal rampart contours

on the width of the gap (2) Considerable variation was observed in both sexes and especially in females and young subjects as has also been noted by previous authors (4) No conclusions about the significance of the width of the gap could be drawn since variations between individuals were greater than between age groups

Changes Suggesting Abnormality in Non Arthritic Subjects

To obtain a more accurate view of the localization of any abnormalities in or around the symphysis the area under investigation was di

vided into four sub-areas on each side as follows A the bony margins of the symphysial face B and C the bony edges from the upper and lower extremities of the face 2 cm laterally and D the inner part of the symphysial bone itself up to a depth of 2 cm Results of this study are presented in table II Changes which were regarded as abnormal and suggestive of a pathological process were more frequent in the female subjects than in the males Both diffuse contours and clear-cut erosion were observed to be more frequent with increasing age It is noteworthy that these changes were mostly encountered near the upper extremity of the symphysial face and were uncommon around the lower extremity

Symphysial Changes in RA and in Ankylosing Spondylitis

From the standpoint of x ray anatomy no distinct difference in the gross appearance of the symphysis was visible between normal and arthritic patients On the contrary they were found to follow a similar pattern of metamorphosis except in some cases of ankylosing spondylitis in which the destruction was too extensive to allow accurate observation. However minor changes were considerably more frequent in the arthritic group than in normal patients Especially the female RA patients of over 40 showed a relatively large number of diffuse bone margins and a small degree of erosion in all the areas investigated In contrast to the changes in the non arthritic patients the RA patients usually showed bilateral changes In RA the upper extremity and the upper edge of the symphysis as well as the margins of the joint gap seemed to be relatively more often involved than the lower extremity or the whole joint (Table II figs 4—6) In the male rheumatic subjects who were only 11 in number such changes were not seen

Tomography revealed changes not visible in ordinary radiographs This was because the lesions were situated on either the interior or the posterior aspect of the joint instead of involving the whole depth of the bone (Fig 7)

In ankylosing spondylitis the erosive changes when present were more extensive and appeared at an earlier age Usually such changes were only seen in patients with a history of ankylosing spondylitis lasting several years In fact the RA changes also appeared as a late sign, usually after disease of a chronic type generally with a history of more than five years



Fig. 4. Pubic symphysis of a 64-year-old female with erosion in the upper part of the joint margins. A history of RA for eight years.

Fig. 5. Small but clear-cut erosion of the pubic symphysis. 65-year-old female with a history of RA for eight years.

Fig. 6. Sclerosis and slight erosion in the symphysis of a 60-year-old female with a history of RA for nine years.

Fig. 7. Tomography of the symphysis showing erosion and osteoporosis in limited areas next to the joint gap. In ordinary radiograms these changes are superimposed by the prominent ventral rampart.

DISCUSSION

Except for the temporary changes caused by pregnancy and to some extent the changes typical of ankylosing spondylitis the pubic symphy

ss as a site of articular changes is largely neglected in routine radio graphic investigation The involvement of this joint, as judged on the basis of the present material is not infrequent in RA, but the changes are usually indistinct and their evaluation requires experience since similar changes sometimes occur in patients with no history of arthritis

The present study emphasizes the importance of knowledge of the post adolescent symphysial metamorphosis which influences its radio graphic contour In contrast to most other joints the pubic symphysis undergoes continuous changes, which up to the age of 40 seem to be related to the normal process of bone maturation Soon after the completion of maturation and sometimes concomitantly with it changes typical of senile degeneration are apt to occur The late maturation of the symphysis is obviously related to the reproductive period of life However it is remarkable that changes in the male joint follow basically the same time sequence although it is only in females that the structure of the symphysis is of primary functional importance

Overlapping of both metamorphosis and degeneration on the one hand and certain pathological processes on the other may in some situations give rise to error as regards the diagnostic changes Small changes such as are observed in RA do not seem to be visible in x ray pictures until old age Thus the symphysis seems to be involved relatively late in RA and even then less frequently than a somewhat similar articulation the manubrio-sternal joint (1 3) as judged from ordinary gross radiography However this may only be partially true since minor changes in bony margins may not be visible before the completion of metamorphotic bone increments after the age of 40

As judged from tomographic studies the difficulty of evaluating whether changes have occurred in the symphysis is at least partly due to the combined effect of the small size of the erosions and the disturbing effects of the ventral and dorsal ramparts which do not allow good visualization of the bone structure next to the joint surface without the use of tomography The relative infrequency of symphysial involvement in RA as reported in the present study as well as in earlier reports may be partially due to the fact that many of the minor changes are impossible to detect with ordinary radiography Thus elucidation of the true frequency of symphysial involvement in RA calls for the use of either tomography or preferably histological verification



Fig 4 Pubic symphysis of 64 year old female with erosion in the upper part of the joint margins A history of RA for eight years

Fig 5 Small but clear cut erosion of the pubic symphysis 65 year old female with a history of RA for eight years

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Larsen Arvi Acta Rheum Scand 17 295—303 1971

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REITER S SYNDROME — A REPORT ON FOUR WOMEN

By

ARVI LARSEN

Summary Four women three of whom are sisters, developed Reiter s syndrome in 1944 after dysentery Twenty six years later one of them is symptomless, one has transitory joint symptoms, while two present hammer toes and radiological signs of sacro-iliac joint involvement one of the two has recurrent iritis and syndesmophytes. Proximal interphalangeal joint ankylosis of one toe is found in two cases Early osteoarthrotic changes are reported

The significance of the familial tendency of Reiter s syndrome is discussed with special reference to the role of inherent and exogenic etiological factors

Many papers (2 3 4 5 11 12) have shown that a minority of male patients with Reiter s syndrome (RS) later develop a disease with clinical and radiological similarities to ankylosing spondylitis (AS) Recently Sairanen et al (15) have come to a similar conclusion in post dysenteric RS Little is known about the course of RS in women due to the low incidence in females (less than 10 per cent compared with that of males) According to one report (10) the clinical course of RS in females is similar to that in males but definite AS was not a sequel The author has had an opportunity to study four female cases 26 years after the onset of dysentery and RS

EPIDEMIOLOGICAL ASPECTS AND METHOD

An 18 year old female (patient A) was working as a charwoman during the war in June 1944 at a military hospital in Finland She contracted

dysentery during an epidemic caused by Shigella flexneri Joint symptoms also developed but for reasons unknown she was not taken to the hospital in which Paronen was collecting his well known material of 344 cases (14) Two weeks after the onset of dysentery she was evacuated to a farm where the three daughters of the farmer (patients B C and D) contracted the same disease (patient A slept with B in the same bed)

Patients A B and C were reviewed by the author Patient D replied to a questionnaire Patients A B and C were submitted to the following studies 1 Clinical examination 2 Radiograms of the hands feet and lumbosacral spine and other joints if affected 3 Laboratory examinations complete blood picture ESR (Westergren) serum uric acid creatinine and electrophoresis rheumatoid factor (Latex and Winblad) antinuclear and anti DNA factors (IF) urine specimen electrocardiogram Further information was obtained about case C who in 1952 and 1955 had been admitted to the Rheumatism Foundation Hospital (RFH)

CASE REPORTS

Case A

Patient A is a 45 year-old married woman who contracted dysentery at the age of 18

One morning during convalescence she found that both knees were swollen and tender During the same day these symptoms developed in the ankles and wrists There were no eye or urinary symptoms Walking was difficult during the next four weeks and she had to use sticks During the following year both ankles were tender and after this, both ankles and the right wrist developed intermittent aches if they became cold or were overstrained Tonsillectomy was performed in 1949 after recurrent attacks of tonsillitis Clinical examination in 1971 showed all joints and the back to be normal Radiogram of the lumbal spine showed a mild degree of degenerative changes Laboratory examinations did not show any abnormalities

Case B

Patient B is a 46 year old married woman At the age of 14 after an attack of tonsillitis one knee became transiently swollen She contracted dysentery at the age of 20

During convalescence most of her joints developed a very severe arthritis Swelling was abundant especially in the ankles where the



Fig. 1. Case C in 1971. Hammer toes which developed in 1944 during the first attack of Reiter syndrome.

skin was tense and reddish. There was high fever for two weeks. Both eyes were deeply red for several days. There were no urinary symptoms. During the next eight weeks she was highly disabled and confined to bed. She found it difficult to open her mouth to eat. For the next eight weeks she was confined to the house and it was eight months before she could attend school. After this because of her tender ankles, knees and hammer toes she found some difficulty in walking. Tonsillectomy was performed in 1947 after recurrent attacks of tonsillitis. The situation remained unchanged until 1969 when she developed an acute joint disease similar to rheumatoid arthritis. At the beginning ESR was 117 and the radiograms of the hands were normal. She was admitted to RFH in 1970 where clinical examination revealed the following data: a mild swelling of the mcp joints, hammer toes, swelling of the ankles and a crepitation in the knees. The back was normal. Radiograms of the hands showed small erosions of some mcp, pip and dip joints. Joint spaces were narrowed in the wrists. Pip-III of the right foot was ankylosed and there were plantar spurs on the calcaneal bones. Mild osteoarthritic changes in the subtalar, knee and hip joints were seen. The sacro-iliac joints showed irregularity and sclerosis. Laboratory examinations: ESR



Fig 2 Case C in 1971 Ankylosis of the proximal interphalangeal joint of the third toe The same pattern was also noted on x ray in 195

22 all others were normal Keller s operation and resection of the meta tarsal heads of both feet were performed with good result A microscopic study revealed fibrosis in the synovial tissue without any sign of inflam mation

Case C

Patient C is a 42 year old unmarried woman who contracted dysentery at the age of 15

Eight days after the onset of diarrhea joint symptoms and con junctivitis developed and their severity during the acute stage was similar to case B She had marked dysuria Later she had the same deformities of the feet and difficulties in walking as case B Tonsillectomy was per formed in 1950 because of pharyngitis She was admitted to RFH for the first time in 1952 Only the disabilities mentioned above were found ESR was 12 and there was no sign of inflammation in the joints There was a second admission in 1955 when hydrops of both knees, swelling of both ankles and tenderness of the back were observed lasting eight weeks ESR was 111 Urine specimen showed recurrent pyuria without bacteria An iritis developed There was spontaneous remission of all



Fig 3 Case C in 1971 Deformed talus with marginal lipping The same pattern was seen in 1952

these inflammatory symptoms Later schizophrenia developed in 1955 and leucotomy was performed in 1958 There were recurrent attacks of iritis in 1964 1965 and 1968 without exacerbation of the joint symptoms Clinical examination in 1971 showed hammer toes (Fig 1) tenderness of the ankles crepitation in the knees and a normal back Radiograms of the hands were normal but ankylosis of pip III was observed in the left foot (Fig 2) as was also osteoarthritis in the ankles with plantar spurs (Fig 3) and osteoarthritis in the knees (Fig 4) In the sacro-iliac joints there were erosions and partial obliteration Th XI XII and th XII LI showed small syndesmophytes on one side (resembling the pattern in AS) Laboratory examinations ESR 28 antinuclear factor +4 (slight elevation) and in the urine sediment there were 10—20 leucocytes per field without bacteria

Case D

Patient D is a 39 year old married woman who contracted dysentery at the age of 13

For two weeks both ankles were swollen and tender The right mcp III was swollen and the skin was discoloured The eyes had a gritty sensation After this she has had no further *joint* symptoms



Fig. 4. Case C in 1971. The left knee with osteophytes which were not seen in 1955 during the second attack of Reiter's syndrome.

DISCUSSION

All the patients developed RS in early to late adolescence. Patient D who had a mild joint inflammation is now symptomless. Patient A whose arthritis was slightly more severe had later transitory joint symptoms. Patient B who had severe arthritis and conjunctivitis later developed hammer toes, osteoarthritis and sacro-iliitis. Patient C who had severe arthritis, conjunctivitis and urethritis later developed additional symptoms of syndesmophytes and recurrent iritis. There is an obvious correlation to be drawn between the severity of the acute stage and residual changes. This kind of correlation has been proposed previously (9). It could be claimed that only case C presents a true RS with the full triad. On the basis of the epidemiology all the four cases must belong undoubtedly to the same category of disease.

These four women and the seven women included in Sairanen's material (15) contracted dysentery during the same epidemic. If we take all these cases as one group it can be stated that four of eleven women were later on symptomless, four developed transitory joint symptoms, three developed sacro-iliac changes of different degrees, including complete

ankylosis one of these three developed syndesmophytes and two recurrent iritis None of them presents a clinically and radiologically full picture of AS Extensive studies (6 7) have shown that female AS gives rise to milder clinical and x ray symptoms in the spine than male AS Therefore it might be justifiable to propose that the prognosis of RS after dysentery is the same in both sexes concerning the tendency to develop symptoms similar to AS

Patient B developed a disease with criteria of seronegative definite rheumatoid arthritis (RA) 25 years after RS The correlation between RS and RA remains obscure

Ford (3) has described the hammer toe deformity as well as the typical radiological changes of talus and calcaneus after venereal RS The present study shows surprising similarities In Sairanen s entire material hammer toes were found only in three cases An interesting detail concerning hammer toes (Fig 1) is a pip ankylosis (Fig 2) in cases B and C This pip ankylosis can be seen in a radiogram from case C taken in 1952 When we further take into consideration that the hammer toe deformity appeared in cases B and C after the first attack of RS it is probable that the ankylosis arose at the same time as the hammer toes This kind of ankylosis is hardly congenital (8) The author has found the following reports on radiological ankylosis of the diarthrodial joints in RS A dip joint of one toe (13) two pip joints of one hand (17) and a hip joint (15) In the first two reports there was a radiological demonstration that ankylosis developed in less than six months and the cases presented a full triad of RS clinically Thus it seems possible even though exceptional that one attack of RS can lead to an ankylosing process of the small joints

In case C we see a deformed talus with marginal lipping (Fig 3) which was first noted at x ray in 1952 We can conclude bearing in mind the severe arthritis of the ankles that this is also a result of the primary RS Distinct osteoarthritic changes can also be seen in the knees (Fig 4) but these were faint in 1955 during the second attack of RS In case B clear osteoarthritic changes in the feet knees and hips could also be seen radiologically In these two patients RS has given rise to early osteoarthritic changes

An interesting finding is the familial appearance of RS The incidence of RS in dysenteric epidemics has been 0 2—1 5 per cent (14 9) In Paronen s study the development of RS in relatives was documented In one family five of seven children infected by dysentery developed RS

in another family two sisters presented both diseases in a third family two brothers contracted dysentery and both of them developed RS although they were living at different places and in a fourth family two of four members who had had dysentery developed RS This kind of familial tendency is scarcely accidental in an epidemic in which 150 000 persons contracted dysentery and about 550 developed RS It seems likely that persons who develop RS have a genetically determined altered response to a certain agent That agent could be either a micro organism or an altered tissue component caused by the infection In the former case the pathogenesis of RS would be analogous to that supposed to exist in rheumatic fever in the latter to that found in an autoimmune disease Since tissue damage in colon or urethra is a common feature preceding RS and since micro-organisms responsible for the tissue damage in cases of RS are different an autoimmune mechanism would be a better alternative In any case RS *after dysentery must have something to do with the* immune response caused by the dysentery especially since RS develops in the convalescence period and usually during the primary immune response Whatever the concept of the pathogenesis is it has to explain very extensive destructive changes including perhaps an ankylosing joint process during the primary RS and the perpetuation of the process to a symptomatology like AS

Although a familial tendency in AS has been reported (e g 7) genetic factors are not regarded as the only ones in the etiology (1) It seems possible that dysenteric infection is one of the exogenic etiological factors In this connection a highly interesting case that has been reported (16) concerned a woman who contracted dysentery during the 3rd month of her pregnancy Later on she developed a symptomless sacro iliitis and *recurrent iritis A son was born who at the age of 11 developed a* recurrent arthritis of the ankles and knees with progression to definite active AS at the age of 18 There is a possibility of the fetal contraction of RS with later development of AS

Although Patients B C and D were relatives and the exogenic factor was the same they developed different forms of RS After the same dysentery epidemic seven men developed a bamboo spine indistinguishable from definite AS (15) Thus the exogenic factor in RS can be attributed only a precipitating role and genetic factors will presumably direct the future course of the disease

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RECURRENT VIRUS INFECTIONS IN IDENTICAL TWINS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

By

O Koivisto E Sotaniemi and T Vesikari

Summary Identical twins with systemic lupus erythematosus are described Serological abnormalities were noted in their living relatives Both patients had a history of recurrent virus infections over a period of several years before SLE became manifest The most striking finding in their viral antibody status was a high titer of measles complement fixing antibodies in both twins In the discussion, attention has been paid to the possible significance of infectious diseases in the etiology of SLE

INTRODUCTION

Some case reports on the occurrence of systemic lupus erythematosus (SLE) in identical twins have been published (1—6) These cases and the serologic findings in relatives of SLE patients (7) suggest a genetically determined predisposition in the etiology of SLE

The possible role of virus infection in the etiology of SLE has drawn attention more recently as a result of animal disease models (8 9) Furthermore recent studies on man have revealed virus like structures in the renal biopsies of SLE patients (10) and high titers of myxovirus antibodies in patients with SLE and Reiter s syndrome (11)

Our report here covers one more pair of female identical twins with SLE. We want to emphasize the history of virus infections before the manifestation of SLE.

CASE REPORTS

Twin 1

A 32-year-old woman was admitted to Oulu university hospital in July 1970 for swelling of the finger joints, joint pains and fatigue.

She had been healthy until the age of 13 (1951), when she became recurrently feverish and her general condition deteriorated. Though treated with salicylates and penicillin, she continued to be feverish and was admitted to a tuberculosis sanatorium for examination. She had peripheral paralysis of the left nervus facialis. The roentgenogram of the chest showed fibrous infiltration connected with the left hilus in the lower lobe and elevated ESR (40 mm/h). The TB cultures were always negative. She was treated for mild pulmonary tuberculosis in the sanatorium for three years. Antituberculous medication was attempted, but she developed a fever reaction and rash on every attempt, for which reason medication had to be discontinued. In 1952, her left n. phrenicus was cut and an artificial pneumothorax was made on the left side. During the following years she suffered recurrently from sore throat. Therefore tonsillectomy was performed in 1957. During the years 1964—1969 she was absent altogether 29 times from her work as needlework instructor at a mental hospital because of various diseases. The diagnoses from this period were carefully recorded on the patient card by the staff physician. In addition to respiratory infections she was recorded to have experienced attacks of measles, rubella and herpes zoster as well as mumps-like parotid swelling on three different occasions. All through this period she had ESR values of 40—60 mm/h and was continuously leucopenic: total leucocyte count varied from 1 600 to 2 400. She was treated with salicylates and antibiotics.

In 1969 she had dysuria and swelling and pain in the hand and foot joints. The findings at both gynecological and urological examinations were normal. In 1968 she became pregnant for the first time, but miscarried. After that her menses were irregular.

Examination in July 1970 revealed her general condition to be relatively good. She was 165 cm tall and weighed 66.5 kg. The left eyelid

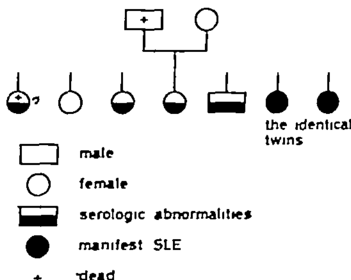


Fig 1 Family investigations of reported twins

was reddened and swollen, and it was slightly ptotic. The left corner of the mouth was weaker than the right (in the anamnesis a paresis of n. facialis in 1951) Otherwise the skin was healthy A few moving painless lymph nodes of the size of a finger tip were palpable on the neck. Blood pressure was 150/90 mmHg and the pulse was steady and regular with a frequency of 70 per min The breath sounds of the left lung base were diminished but otherwise the auscultatory findings of the lungs and the heart were normal Liver and spleen were normal in palpation. The finger joints of both hands and the right ankle ball of the foot, and phalangeal joints were swollen and tender

Blood group was 0 Rh negative (C D E c+ MNSs P_1 Le (a+b-) Fy (a-b+) K) ESR was 57 mm/h. Hb 15 2 g per 100 ml, MCHC 29 % Leucocyte count was 2 400 with 3 % band neutrophils 35 % segmented neutrophils 2 % eosinophilic, 44 % lymphocytes 16 % monocytes and 0 % basophilic. Thrombocyte count was 195 000 per c.mm

Liver function tests and serum electrolytes were normal Total serum protein was 7 7 g per 100 ml Electrophoresis revealed albumin 53 4 % alpha 1 globulins 1 7 % alpha 2 globulins 10 8 % beta 1 globulins 5 8 %

beta ? globulins 5 0 % gammaglobulins 23 3 % Serum immunoglobulins were quantitated by radial immunodiffusion and the following values obtained IgG 1720 mg per 100 ml IgA 320 mg per 100 ml and IgM 100 mg per 100 ml LE cell tests were twice positive Coombs test, cold agglutination cryoprecipitation and cardiolipin were negative RA Latex was negative Waaler Rose negative AST 400 and ASTA below 2 Antinuclear factors were positive by immunofluorescence nucleic acid antibodies negative Urinanalysis was normal

Bone marrow was normal EKG showed T wave inversion inleads III and aVF

Roentgenological examination revealed elevation of the left diaphragm and atelectasis in the left lung base The size and the shape of the heart were normal No changes typical of RA were noted in the hands or feet The patient was treated with chloroquine salicylates and cortisone After a couple of months her subjective condition had improved so much that she could return to her previous work

Twin 2

A 32 year old woman who came to be examined on request in August 1970 She had been healthy until the age of seven (1945) when she had pneumonia Since 1955 she had recurrent infectious diseases and tonsillitides tonsillectomy was performed in 1959

In February 1965 she had a normal childbirth One month after the delivery she was admitted to hospital for fever and ache in the left ankle knee and hip joints and both shoulder and wrist joints which were also painful to move The following laboratory findings were then obtained ESR 31 mm/h AST 640 Waaler Rose negative RA Latex and LE cell tests negative Leucocyte count was 1 700—>400 urinanalysis showed leucocytes and p ote nuria She was treated with penicillin and salicylates and the symptoms disappeared The symptoms reappeared one year later when she had fever and arthralgia after suffering from a sore throat She was re admitted and the following values were obtained ESR 70 mm/h leucocytes 6 400 RA Latex negative Waaler Rose negative and LE cell test three times negative She was again treated with penicillin and salicylates She continued however to have subjective symptoms for ten months which time she had to be absent from work

During the following two years she consulted a doctor several times for fever and arthralgia ESR remained high 30—60 mm/h and in

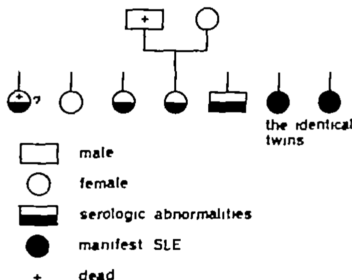


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During the following two years she consulted a doctor several times for fever and arthralgia ESR remained high 30—60 mm/h and in

1969 LE cells were found for the first time She was treated with chloroquine and salicylates In March 1970 she was again admitted to hospital for fever and joint pains Now LE cells were detected three times Antinuclear antibodies and cryoprecipitation were present She received chloroquine and prednisolone as medication and she was considered incapable of work

Examination in August 1970 revealed her general condition to be good She was 169 cm tall and weighed 74 kg Small eruptions of blood were noted on the back otherwise the skin was healthy Palpable lymph nodes were not noted Blood pressure was 140/100 mmHg The auscultatory findings of the heart and the lungs were normal Liver and spleen were normal in palpation Neurological status was normal with the exception of the ulnar surface of the right arm in which skin sensitivity was decreased (accident in 1955)

Her blood group was the same as that of twin 1 Hb was 12 9 g per 100 ml ESR 49 mm/h Leucocyte count was 5 700 with 0 % band neutrophils 61 % segmented neutrophils 2 % eosinophilic, 0 % basophilic 5 % monocytes and 32 % lymphocytes Thrombocyte count was 270 000 per c mm Liver function tests and serum electrolytes were normal AST was 800 and ASTA below 2 Waaler Rose and RA Latex tests negative, LE cells were found in three specimens and antinuclear antibodies were positive by immunofluorescence method Coombs test and cryoprecipitation test were negative Total serum protein concentration was 6 7 g per 100 ml serum electrophoresis showed albumin 50 % alpha 1 globulins 1 3 % alpha 2 globulins 15 4 % beta 1 globulins 7 4 % beta 2 globulins 4 1 % gammaglobulins 23 6 % A quantitative serum immunoglobulin determination showed IgG 2 300 mg per 100 ml IgA 112 mg per 100 ml IgM 84 mg per 100 ml Urinanalysis was normal The lungs and the heart were normal in roentgenological examinations Roentgenograms of the joints showed no rheumatic changes

Family investigations

The father of the twins had died of a cardiac disease at the age of 78 One sister had died of cerebral hemorrhage, which diagnosis had been confirmed by autopsy Her right kidney was found to be almost completely destroyed the microscopic investigation provided a picture of chronic glomerulonephritis

The mother three sisters and one brother who were alive were subjected to investigations involving serum electrophoresis immunoelectro

TABLE I

Viral Antibodies in Identical Twins as Measured by Hemagglutination Inhibition (HI) and Complement Fixation (CF) Techniques

HI Antibodies	Twin 1	Twin 2
Influenza A	1 80	1 40
Parainfluenza 1	1 1 280	1 160
Mumps	1 80	1 20
Rubella	1 160	1 160
Measles	1 20	1 40
CF Antibodies	Twin 1	Twin 2
Influenza A 2	1 16	1 16
Parainfluenza 1	1 32	1 16
Parainfluenza 2	1 8	1 16
Parainfluenza 3	1 64	1 8
Respiratory syncytial virus	1 128	1 8
Adenovirus	1 8	1 32
Herpes simplex	1 64	1 16
Varicella zoster	1 8	1 8
Measles	1 256	1 128

Low CF titers (1 8 or less) were found for the following antigens poliovirus reovirus, cytomegalovirus vaccinia mumps rubella and mycoplasma pneumoniae

phoresis Waaler Rose RA Latex nuclear antibodies and LE cells The mother was 80 years old and healthy the findings of the laboratory tests were normal The brother was subjectively healthy positive Waaler Rose (+1/180) was noted as an abnormality Two of the sisters suffered from arthralgia one of them had antinuclear antibodies the other had normal findings One of the sisters was subjectively asymptomatic but was found to have antinuclear antibodies

Viral antibody determinations

The sera of both twins were tested for the presence of antibodies to various viral antigens and the results are compiled in Table I

The hemagglutination inhibiting (HI) antibodies were titrated using influenza A2 parainfluenza 1 mumps measles and rubella antigens Twin 1 had a high titer of parainfluenza 1 antibodies (1 1 280) consistent with a recent infection by this virus Both twins had HI antibodies to all the tested viruses but no other notably high titers were found The

— 2

sera were also fractionated by sucrose gradient centrifugation (12) and the rubella and measles HI antibodies were detected only in the 7S fraction which conventionally is indicative of old immunity

Complement fixing (CF) antibodies were determined using a number of virus antigens Both twins possessed influenza A2 parainfluenza adenovirus and herpes simplex virus antibodies and twin 1 had a high titer of respiratory syncytial virus antibodies More strikingly both had a high titer of measles antibodies (1 256 and 1 128 respectively) The antigen used in the titration was prepared from a measles infected cell pack of Vero cells (a continuous green monkey kidney cell line) Neither of the twins had demonstrable antibody to control antigen prepared from uninfected Vero-cells

DISCUSSION

The probability that these women were identical twins was supported by their appearance their sex and their identical major and minor red blood cell groups Skin grafting was not done The diagnosis was confirmed by the anamnestic data clinical examination positive antinuclear antibodies LE cells and the disappearance of subjective symptoms after immunosuppressive treatment

Serological abnormalities were noted in all but one of the living siblings of the twins The chronic glomerulonephritis of the sister who had died suddenly of cerebral hemorrhage may have been based on SLE She had spent the last years of her life away from her relatives for which reason no reliable anamnestic data could be obtained At any rate the relatives of the twins clearly showed marks of serological abnormality which agrees well with the number of studies previously made on relatives of SLE patients (4 5) It is very interesting to note that our patients had a great number of virus infections before the manifestation of SLE Data of twin 1 recorded by a staff doctor show that during the years 1964—1969 she had measles rubella herpes zoster mumps on three different occasions and several times common cold

Virus serologic studies showed that she had antibody to all the mentioned viruses but only the parainfluenza 1 HI titer and the respiratory syncytial virus CF titer were considered exceptionally high In addition to these both twins had an elevated measles CF antibody titer but the measles HI antibodies were not elevated in the same proportion

Thus the serologic findings are only partially consistent with the history of virus infections as high titers of rubella or mumps antibodies were not detected and of the measles antibodies only the CF titer was high. At present it is impossible to state if the recorded fairly easily recognizable diseases were caused by the specific agents. If this were the case, the serologic findings would suggest a modified immune response to these viruses.

The elevated measles and parainfluenza 1 antibodies in the twins are in accordance with previous studies on SLE patients (11 13). However in another study of Finnish patients with SLE it was found that both the measles HI and CF antibody titers were higher than in the control population (14).

It apparently is much too early to name a single virus as a possible candidate to have some role in the pathogenesis of SLE. Still suggesting that virus may have a role one has to consider the possibilities of recurrent infections by many agents as well as a modified infection by one or few agents.

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ANKYLOSING SPONDYLITIS

Report of One Case Studied with Histology Tetracycline Bone Labelling Microradiography and Scanning Electron Microscopy[1]

By

H Inoue[2] H Julkunen and K Vainio

Summary One autopsy case of ankylosing spondylitis was studied with histology tetracycline bone labelling microradiography and scanning electron microscopy A focus of inflammatory cells was found beneath the anterior periost of a lumbar vertebral body and early marginal syndesmophytes were demonstrated by histology and microradiography Tetracycline bone labelling showed new bone formation within osteo phytes attempting to bridge an intervertebral facet joint Scanning electron microscopy showed degeneration of femoral head articular cartilage while articular cartilage of an unfused portion of a sacro iliac joint showed no definite changes with respect to equivalent controls

Histological details of 59 post mortem cases of ankylosing spondylitis have been published (1) since the initial report of Siven (6) The charac teristic early finding is a periarticular inflammatory cell reaction (5 6) with later increased granulomatous tissue and ossification The ossifica tion may be periostal or represent enchondral metaplasia (2) Increased connective tissue with new bone formation may also be found in the cancellous spaces of sclerotic bone adjacent to the sacro iliac joints in early and active cases (4)

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Fig 1 Roentgenogram showing complete fusion of the right and partial fusion of the left sacro-iliac joint



Fig Inflammatory cell infiltration (arrow) in the periost of anterior part of the vertebral body Sp a 78 years H & E 40 x



Fig 3 Syndesmophyte (arrow) in the corner of the vertebral body 1 = anterior longitudinal ligament 2 — annulus fibrosus H & E 40 x

This paper will present pertinent autopsy findings from a single presumed case of ankylosing spondylitis studied by ordinary light microscopy tetracycline bone labelling microradiography and scanning electron microscopy

CASE REPORT

A 78 year-old retired foreman sustained multiple fractures when struck by an automobile and died eight days later He was given intramuscular tetracycline 1 gram per day during the eight-day period to combat pulmonary infection while supported on a respirator Roentgenograms showed complete fusion of the right sacro-iliac joint and partial fusion of the left (Fig 1) There was bony bridging between cervical vertebrae 5/6 and between thoracic vertebrae 11/12 The hip joints showed decreased joint spaces with marginal osteophyte formation No previous history of back or hip disability was obtainable

At autopsy specimens were taken from the unfused portion of the left sacro-iliac joint and from the lumbar vertebrae 3/4 Specimens of articular cartilage for scanning electron microscopy were taken from both



Fig 4 Probable ossification site near the corner of the vertebral body with destruction of the trabeculae (arrows) 1 = anterior longitudinal ligament — discus Microradiograph 40 x



F 5 Microradiographic picture of the intervertebral joint 1 and 2 = bridge formations 3 = cartilage 10 x



Fig 6 Tetracycline fluorescence (arrows) in the top of bridge formations Inter vertebral joint Same area as in fig 5 10 x

sides of the unfused portion of the left sacro iliac joint and head of the left femur Control specimens of articular cartilage from the femoral head and the sacro iliac joint were taken from two males 70 years and 75 years old following sudden deaths from pulmonary embolism and myo cardial infarction respectively

METHODS

Specimens for histology were decalcified with EDTA and stained with hematoxylin eosin Undecalcified specimens were embedded in methyl methacrylate ground to a thickness of 100 μ and studied under ultraviolet light for tetracycline fluorescence Microradiographs were obtained by the method earlier used by Julkunen and Rokkanen (4)

Specimens of articular cartilage were gently washed in saline fixed in 10 % neutral formalin dried with increasing concentrations of acetone and stored at —18 degrees centigrade Scanning electron microscopy was performed using the Stereoscan (Cambridge) apparatus (by Mr H Ek lund M A Finnish Paper and Pulp Research Laboratory)



Fig 7 Histologic picture of the cartilage of the left sacro-iliac joint A = sacral side B = iliac side Sp 4 H & E 40

RESULTS

A focus of inflammatory cells was found beneath the anterior periost of the lumbar vertebra (Fig 2) Syndesmophyte formation was evident on the anterior corner of the lumbar vertebra protruding into the anterior longitudinal ligament with no sign of inflammatory response (Fig 3) The microradiograph (Fig 4) shows possible early ossification of a

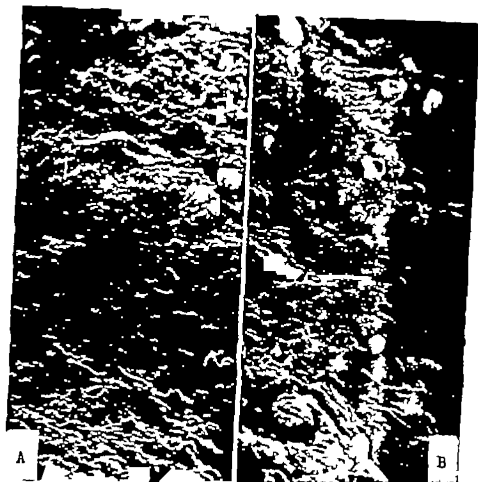


Fig 8 Scanning electron micrograph of the surfaces of the sacro iliac joint Sp A = sacral side 000 × B — ilia sid 1 000

syndesmophyte on the outer corner and destruction of bony trabeculae within the inner corner of the lumbar vertebral body

The bony bridging proceeding across the lumbar intervertebral facet joint in the microradiograph (Fig 5) shows tetracycline fluorescence *within the tips of the bridging osteophytes* (Fig 6)

Articular cartilage from the sacral side of the unfused portion of the left sacro-iliac joint was relatively normal under light microscopy (Fig 7 B) On the iliac side the cartilage showed superficial desquamation and cloning of cartilage cells (Fig 7 B) Scanning electron microscopy of

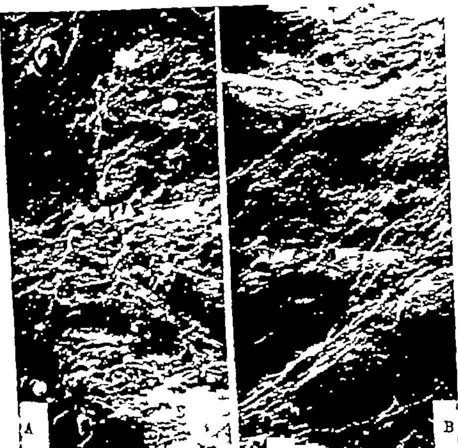


Fig 9 Scanning electron micrograph Sacro-iliac joint. Control 70 years A = sacral side 600 x, B = iliac side 600 x

both articular surfaces produced equivalent patterns similar to control specimens (Figs 8 A—B 9 A—B) Numerous small pits possibly representing nutritional canals may be seen on the surface of the cartilage (Fig 10)

Scanning electron microscopy of articular cartilage from the left femoral head showed deep hollows with fraying and separation of the exposed collagen bundles (Fig 11) The control specimen (Fig 12) exhibited gentle surface undulations typical of a spherical articular surface (3 7)



Fig. 10. Scanning electron micrograph. Sacral surface of the sacro-iliac joint. Sp. a
20 000 x

DISCUSSION

The etiology of ankylosing spondylitis remains unknown. Hereditary influences and sepsis arising from urogenital organs or gut have been suggested as contributing factors.

Lymphographic studies of the retroperitoneal region adjacent to the vertebral bodies showed chronic inflammatory changes in seven of twelve cases of ankylosing spondylitis (8). In the present study a focus of inflammatory cells was found beneath the anterior longitudinal ligament which supports the lymphatic transfer theory, particularly as this man was known to have a chronic urinary tract infection.

The microradiographs and tetracycline fluorescence demonstrate ossification at the margins of a vertebral body and across an intervertebral facet

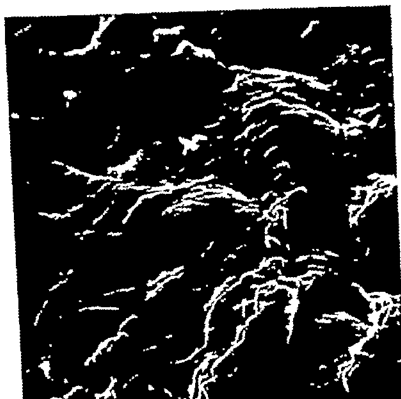


Fig 11 Scanning electron micrograph of the surface of the femoral head Note the hollow formation and separation of the collagen bundles Sp 500 x

joint which is not specific for ankylosing spondylitis No new bone formation was found within the cancellous spaces of sclerotic bone adjacent to the sacro-iliac joint similar to that found in biopsy specimens from early and active cases (4) The advanced age of this man with low activity of the spondylitic process may explain the discrepancy

Scanning electron microscopy studies of the articular cartilage surfaces in ankylosing spondylitis have not been previously reported The sacro-iliac cartilage was found to be similar to control specimens while the femoral head specimen showed marked degenerative changes These degenerative changes in the femoral head articular cartilage are similar to those seen in osteoarthritis or rheumatoid arthritis and are not specific to ankylosing spondylitis

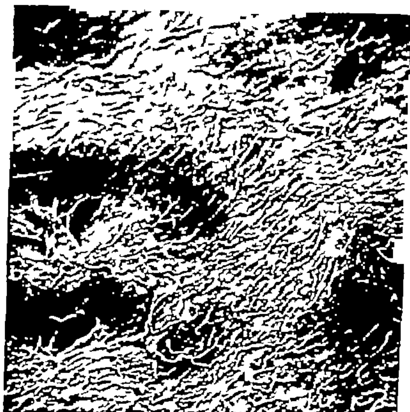


Fig 12 Scanning electron micrograph f the femoral head Control 75 years ?00 x

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